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STUDIES ON THE REJECTION OF THE TRANSPLANTED HOMOLOGOUS DOG LIVER

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IN A CONTEMPORARY REPORT, the technical problems and complications encountered with homotransplantation of the dog liver were described (15). As occurs with other vascularized homografts, the liver appeared to be rejected by the host after a characteristic time interval, usually 6 to 10 days.

The present study is concerned with an analysis of events, both in the homografted liver and the host, in 18 dogs which survived 4 or more days after liver transplantation, long enough presumably for homograft rejection to occur. This included postmortem and tissue studies, as well as chemical and hematologic determinations during life. Strong histologic evidence has been obtained of widespread participation of the host reticuloendothelial system in the rejection, quite comparable to that seen after bacterial and foreign protein immunization.

METHODS

The techniques used for liver transplantation have been previously described (15). The homograft was positioned in the liver fossa, after removal of the recipient dog's liver, and splenectomy was performed. Arterialization and internal biliary drainage were carried out with a uniform technique in all 18 experiments. Venous pathways were reconstructed with three variations: (a) anatomically, 8 cases; (b) anatomically with the addition of a small portacaval shunt, 6 cases; and (c) by diversion of both the splanchnic and vena caval flows through the liver, 4 cases. Although the method used was profoundly influential in determining early mortality, the type of venous connection was not an important factor in most of parameters analyzed in the present study, and the results apply to all dogs, unless otherwise stated.

Adult mongrel dogs were used. The donor and recipient were always chosen for obviously different color and general appearance. In about one-half the experiments, the donor and recipient were different sexes. Blood studies were obtained preoperatively and every 2, 3, or 4 days thereafter, and the removed blood was replaced with immediate transfusion. In a few animals, transfusions were also given for the treatment of late gastrointestinal hemorrhage. All chemical

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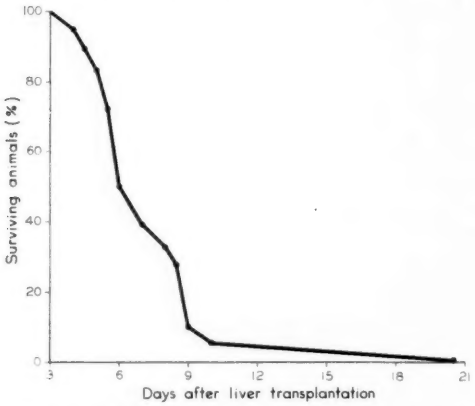


FIG. 5. Survival in dogs living more than 4 days. Note high mortality between fifth and tenth day.

studies were standard determinations, made in a clinical laboratory. Autopsies were performed promptly, usually within an hour and never longer than 8 hours after death, and the specimens fixed in formalin. Hematoxylin-eosin stains were always used, and in some cases additional tissue stains were employed.

RESULTS

Survival. Survival times in 18 dogs are shown in Figure 5. Ninety per cent of the deaths occurred between the fifth and the tenth days. The longest survival was 20½ days. Although many other factors contributed to death, evidence will be presented that graft rejection played an important role in most cases.

Clinical behavior. The dogs with the most satisfactory course were those with anatomic venous reconstruction. They were usually able to eat after the second postoperative day. Diet generally consisted of brown sugar water and bread, but some of the dogs were hungry for and allowed to eat meat. Although the dietary intake of dogs with other than anatomic venous connections was poor, physical activity of the different groups of animals was frequently normal for the first 4 or 5 days.

On the sixth or seventh day, jaundice developed in every experiment, usually within 12 to 24 hours after it was noted that the urine had become dark. Some of the dogs continued to eat, but usually dietary intake was sharply reduced. Jaundice was followed by death in 2 to 4 days in all but 1 animal in which the jaundice receded after the eleventh day. Terminally, pallor of the gums was often seen, and vomiting was common in both feeding and fasting dogs.

The clinical behavior of the longest survivor (No. 65) requires separate comment. Jaundice developed in this animal on the sixth day, and the dog appeared to be critically ill for 4 days. He continued to eat, however, and after the eleventh day improved with continued clinical and chemical regression of the jaundice (Fig. 6) until death after 20½ days. This was the only unequivocal instance of improvement after signs of liver malfunction had occurred.

Rectal temperatures and femoral pulse rates were taken twice a day. All animals had low grade fever during most or all of the survival period. This was seen by the first day after operation and persisted without spikes (Fig. 7). There was no deviation from this pattern during the presumed rejection period. Correspondingly, pulse rates were not subject to wide variation after the immediate postoperative tachycardia had subsided (Fig. 7).

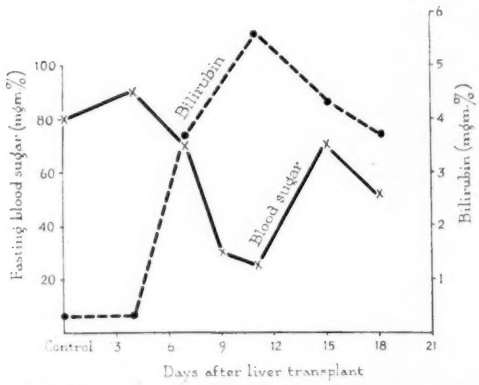


FIG. 6. Blood sugars and bilirubins in 20½ day survivor (No. 65). Note improvement in chemistries after eleventh day.

Most of the dogs lost about .25 kilogram in weight per day after operation. In some cases, the tissue loss was undoubtedly greater, since the development of ascites was often prominent.

Blood chemistry. Fasting blood sugars were obtained before and after operation. Samples were taken in the morning, after an 8 to 12 hour withdrawal from food or intravenous fluids. Initially, blood sugars remained at a normal level. However, at varying times, from 4 days on, blood sugars as low as 15 to 25 milligrams per cent were observed (Fig. 8). With longer survivals, a definite correlation was evident between survival time and degree of hypoglycemia (Fig. 8). In most dogs, a dropping blood sugar was a preterminal event, but in the longest survival the blood sugar fall reversed itself as other liver chemistries improved (Fig. 6).

The time of development of chemical jaundice was very definite. By the fifth day, only 1 dog had a rise in bilirubin, but by the sixth day all tested dogs had become jaundiced (Fig. 9). The increase in the direct bilirubin fraction was less but paralleled the total rise (Fig. 9). Comparable rises were seen with alkaline phosphatase, starting on the fourth or fifth day (Fig. 10).

Total proteins were not predictably altered by transplantation. An example is shown in Figure 11 with determinations from the 20½ day survivor, in which major shifts in either the total or the albumin-globulin fraction did not occur. Thymol turbidity tended to increase, but inconstantly. Blood cholesterol rose (Fig. 12), remained stable, or fell with about equal frequency. Blood urea nitrogen remained normal in all dogs until terminally, when in 3 of 11 animals studied a sharp rise occurred (Fig. 12).

Hematologic studies. Complete blood counts were obtained before and at varying times after operation. Because of transfusions, analysis of erythroid values was not meaningful. All animals, except 1, had rises in the white count, sometimes as high as 40,000.

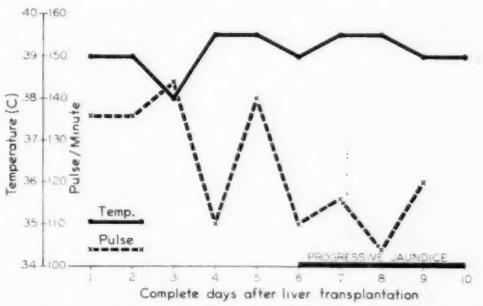


FIG. 7. Fever and pulse of dog 76. Animal had no complications. Cause of death probably homograft rejection.

The rise was specifically due to granulocytosis with a marked neutrophilia. No cellular abnormalities were noted in the peripheral blood, and in particular plasma cells were not seen.

Urine studies. All but 1 of the dogs excreted adequate urine until just before death. In 3 of 8 animals tested, albuminuria developed after 2 to 4 days and persisted. Analysis of bile products disclosed differences in urines collected before and after 4 complete postoperative days. In 8 specimens collected from different animals before the fourth day, bile was detected in only 2. After the fourth day, 13 of 14 urines contained bile. Before

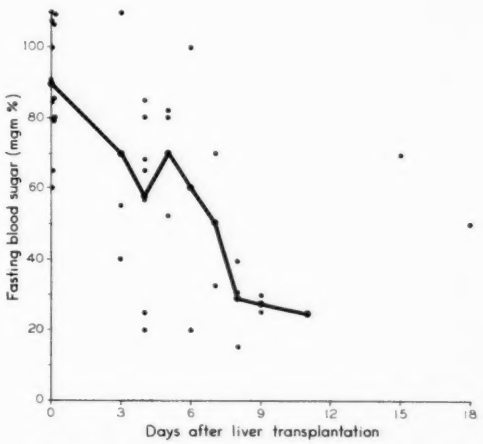


FIG. 8. Fasting blood sugars (dots) in all dogs not treated with intravenous glucose. Solid line connects average values for each day. Note that severe hypoglycemia sometimes developed as early as the fourth day.

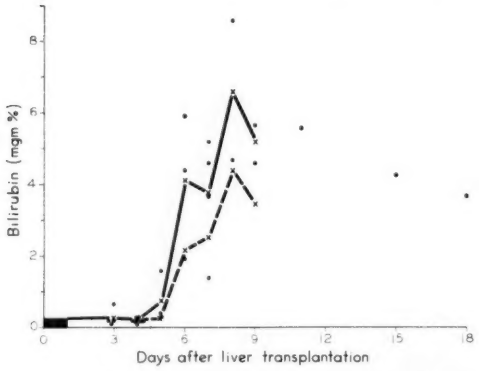


FIG. 9. Scattergram showing pattern of onset of jaundice. Dots are individual total bilirubin determinations. Solid line connects average total bilirubin for each day. Dashed line represents the average of the corresponding direct bilirubin determinations. Note absence of chemical jaundice until sixth day.

the fourth day, half of the specimens contained urobilinogen (more than 1.0 Ehrlich unit), and after the fourth day urobilinogen was detected in only 5 of 14 samples.

Gross pathologic findings. The homografted liver had characteristic gross findings. It was usually larger than normal with a tan appearance and firm consistency. Although it had no other attachments than the various anastomoses, there were no instances of dislocation of the organ from the liver fossa. On section, the tissue cut with a firm and gritty sensation. The transected surface had a nutmeg appearance, such as seen with chronic heart failure. In every case, the cholecystojejunostomy and enteroenterostomy were intact.

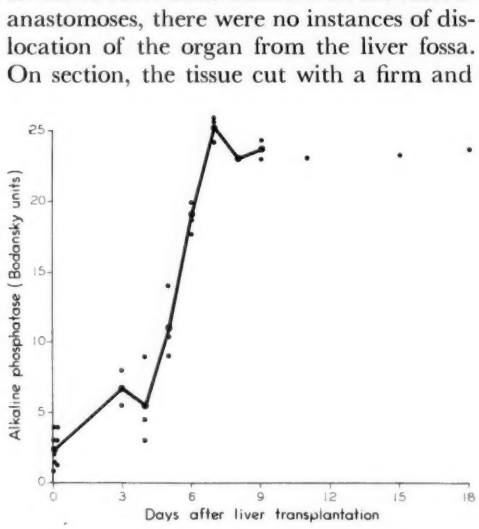


FIG. 10. Alkaline phosphatase levels in 8 dogs. Note marked rise after fourth day.

Thrombosis of a vascular anastomosis occurred in 4 of the 18 experiments, twice in the aortic graft and once each in the portal vein and inferior vena cava. In 1 dog, the aortic suture line disrupted after 5 days. In the 20½ day survivor, aortic rupture may have occurred, but it was not possible to be certain of this at autopsy.

The abdomen contained from 25 to more than 1,000 cubic centimeters of blood-stained fluid. Ascites was most prominent in animals in which both caval and portal flow had been transmitted through the liver. Wound infection, a complication in 5 of the 18 dogs, occurred in animals with severe ascites in which the fluid dissected through the incision. Significant pleural infusion occurred in only 1 dog.

Some of the host organs regularly exhibited gross abnormalities. The lungs invariably had a peculiar firm leathery consistency. In addition, some of the animals had atelectasis, pneumonitis, or pulmonary edema. In 6 of the hearts there was focal epicardial necrosis, the lesions being confined to the right ventricle. Usually, superficial sloughing or ulceration was found in some portion of the gastrointestinal tract, most prominently in the duodenum. In 6 of the 18 dogs, multiple shallow duodenal ulcers were encountered, and in 2 more, duodenal ulcers were almost perforated. The kidneys and adrenal glands were normal. Host lymph nodes in the mesentery, mediastinum, and elsewhere were generally enlarged.

Microscopic findings. As noted previously (15), hepatic architecture was well preserved during the first few days after operation, unless hepatic congestion or other complications of revascularization occurred. After 4 days, alterations developed in all liver homografts which were usually related quantitatively to the period of survival. At first, hepatic cell loss was absent or minimal (Fig.

1). However, even in dogs surviving only 4 or 5 days, a mononuclear infiltrate of plasma cells and lymphocytes appeared. These cells were most prominent in the periportal areas but were also seen diffusely throughout the parenchyma (Fig. 1). Endothelial and adventitial proliferation of small arteries was often seen.

After 6 days, undisturbed hepatic architecture was found in only 1 homograft (dog 20), from a 9 day survivor. The only striking change in this exception consisted of a periportal and diffuse mononuclear infiltrate (Fig. 2), consisting of plasma cells and lymphocytes. In all other experiments, there was more or less extensive hepatic cell loss, sometimes most prominently around the central vein (Fig. 4). In other instances, the parenchymal loss was general and so extensive that residual liver cells could be identified only with difficulty (Fig. 3). The liver was in these cases almost completely replaced with a massive mononuclear infiltrate. Congestion of the homograft completed the picture, often with extravasation of red cells into the structureless tissue (Fig. 3). In a few animals, necrotizing arteriolitis was seen. The presence of bile pigment in the hepatic cells was an inconstant finding (Fig. 4).

The longest survival had homograft changes which were less well developed than many of the 6 to 10 day animals. After 20½ days, a semblance of organized structure remained (Fig. 4). Parenchymal loss was chiefly around the central veins. The diffuse and periportal mononuclear infiltrate, comprised chiefly of plasma cells (Fig. 4), was comparable to that found in the shorter survivals. Many of the intrahepatic bile ducts were denuded of epithelium. Connective tissue stains did not reveal the presence of fibrosis. Reticulum stains showed good preservation of the reticular pattern.

In 7 experiments, enlarged lymph nodes from the posterior mediastinum were studied. In all cases, there was more or less cortical thinning with a decreased number of follicles (Fig. 13) which contained principally lymphocytes and monocytes. Lymph pulp was increased with a large number of plasma cells in the medullary cords. Supporting tissue around the nodes was infiltrated with plasma cells.

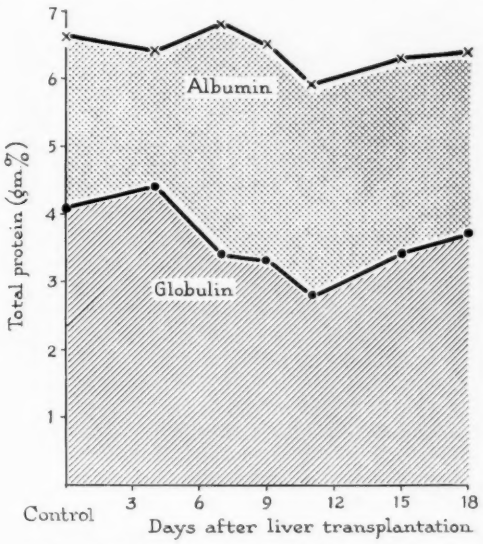


FIG. 11. Total protein and albumin/globulin fractions in dog 65.

Aggregates of plasma cells and other mononuclear cells were found in all host kidneys. These were principally in the cortex, usually in a periglomerular or perivascular position (Fig. 14a). There was endothelial and adventitial proliferation of the small

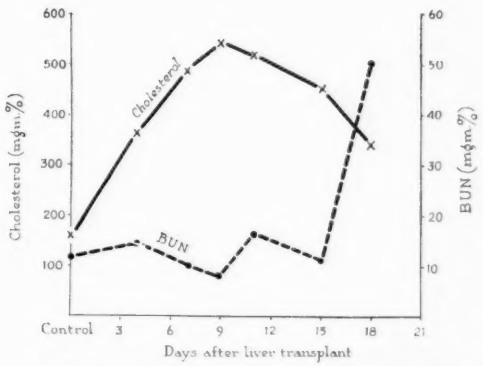


FIG. 12. Cholesterol and blood urea nitrogen in dog 65. Terminal uremia was seen in minority of animals.

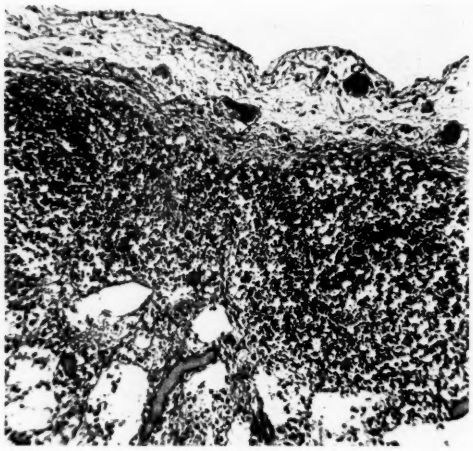


FIG. 13. Mediastinal lymph node from dog 65. × 82. Note cortical thinning.

vessels, often with edema. In one-third of the cases, a more diffuse plasma cell and mononuclear response was also found throughout the kidney. In addition, a moderate to marked plasma cell involvement was noted in the perirenal (Fig. 14b) and periadrenal tissues.

Pulmonary abnormalities included passive congestion, pulmonary edema, atelectasis, and pneumonitis. However, in 15 of 18 experiments, a specific abnormality was noted. There was thickening of the pulmonary alveolar wall, apparently due to endothelial and histiocytic proliferation in the septa (Fig. 15). A light plasma cell infiltrate was usually present in the parenchyma with focal accumulations around small blood vessels. Some vessels had changes similar to those described in the kidney. Multinucleated giant cells were very numerous (Fig. 15).

Bone marrow studies were made. In every experiment, increased numbers of plasma cells and lymphocytes were found. In some cases, these infiltrates were moderate, but in other dogs (Fig. 16) the relative and absolute increases in plasma cells and lymphocytes were striking and extensive.

Skeletal muscle from the foreleg was studied in all 18 dogs. No diffuse or focal plasma cell response was found in any case.

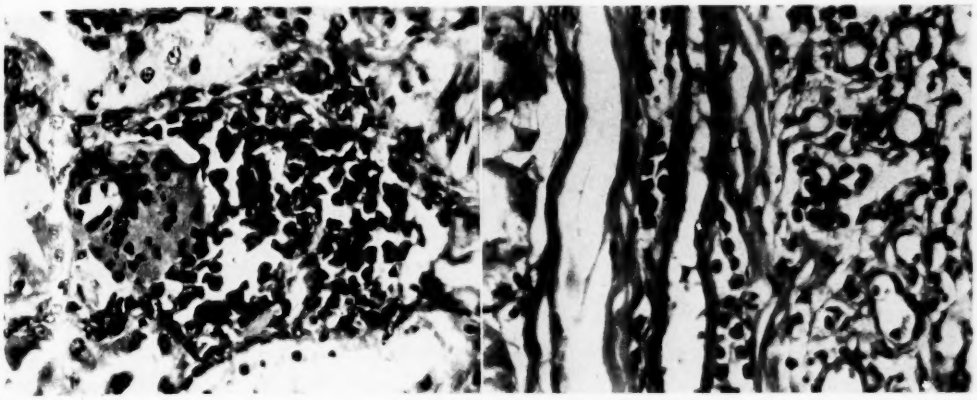
Findings in the heart and gastrointestinal tract were related partially to traumatic artefact. Focal myocardial infarcts often occur as a direct result of operation (15). In the later dogs, organizing infarcts or mononuclear infiltrates were seen in all experiments. In the gastrointestinal tract, hyperemic sloughing and gastritis or enteritis were seen in various experiments. A diffuse plasma cell and lymphocyte infiltration was always present, often to a marked degree.

Causes of death. The precise mechanism of death was often difficult to determine, not only because the findings with homograft rejection are not specific, but because of the frequent coexistence of serious postoperative complications. In 5 dogs, rejection appeared by exclusion of other factors to be the sole reason for death. In all dogs surviving more than 6 days, it was thought that rejection of the homograft was in process at the time of death, in view of the histologic and chemical evidence of hepatic deterioration.

Controls. Three types of controls were available for assessing the role of operative trauma or surgical artefact in the foregoing results. The first of these involved analysis of dogs which died after liver transplantation as the direct result of operative trauma, in from a few hours to a day or so after surgery. In these animals, hepatic architecture was preserved, except when "outflow block" had occurred. There was no infiltrate in the livers. Fresh focal infarcts were found in the myocardium. The histologic changes in the bone marrow, kidney, lymph nodes, and lung described for longer surviving animals were not present.

In 4 control dogs, cholecystojejunostomy with enteroenterostomy was performed after ligation of the common duct. The dogs were sacrificed at 5, 13, 14, and 15 days. Histologic studies of the liver were either normal or disclosed a minimal periportal polymorphonuclear infiltrate. In no case did bilirubin or alkaline phosphatase rise, nor were other chemistries changed. All other organs were normal.

Finally, in 4 more dogs, sham operation



a b

FIG 14. Host kidney from dog 76 showing: a, perivascular mononuclear aggregate of cells and vascular changes, × 232; b, cellular response in perirenal tissue, × 232. Aggregates were mostly plasma cells.

was performed involving autografting the liver. The steps employed were essentially the same as with homograft experiments, except that the dog's own liver was returned to the liver fossa. Postoperative chemical studies did not show the abnormalities described after homografting. The dogs did not become jaundiced or ill. The animals were sacrificed after 7 to 15 days. Focal myocardial infarcts or infiltrations were present in all 4 animals. Liver architecture was completely preserved, and mononuclear infiltrates were not present. The histologic abnormalities noted in the foregoing in the bone marrow, lung, kidney, and lymph nodes were not found.

DISCUSSION

Dempster, Moore and associates (12, 13), and other students of whole organ transplantation have recognized the need for delineating changes ascribable to the presence of a homograft from those alterations which result from surgical trauma. Some nonspecific artifacts were found in the present studies. For example, the control studies indicated that the lesions in the myocardium were explicable by the trauma of massive surgery. However, the changes in the chemistries and the consistently noted pathologic findings in the liver, bone marrow, kidneys, lungs, lymph nodes, and possibly gastrointestinal tract seem clearly related to the placement of the homograft.

The metabolic studies provided a means of following the repudiation of the liver graft by the host animal. It has been shown by Mann and subsequent observers that dogs will die in 1 or 2 hours after hepatectomy if continuous intravenous glucose is not provided. Under the same conditions, continued survival after replacement of the recipient's liver with a homograft was incontrovertible proof of hepatic graft function. Function was complete initially, but measurable deterioration began on the fourth to sixth day, with the onset of jaundice, the rise in alkaline phosphatase, and the tendency toward hypoglycemia. The high direct blood bilirubin component, in conjunction with the elevated serum alkaline phosphatase and urinary bile, suggested obstructive jaundice. Since extrahepatic obstruction was ruled out by control studies, it was concluded that obstruction was diffuse and intrahepatic. Such an occurrence was not hard to envision in view of the distorted, firm, and enlarged liver found at autopsy. In previous studies on liver homografts transplanted into the pelvis, Welch

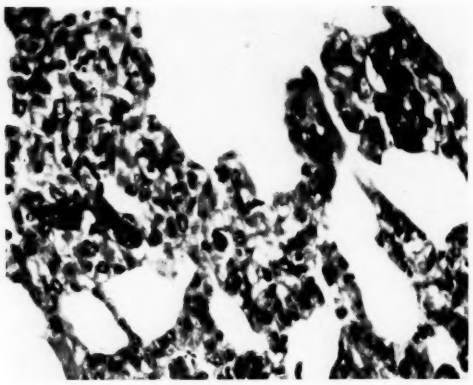


FIG. 15. Host lung from dog 68 showing proliferative process in alveolar septa, and giant cells. × 225.

and his associates (7) noted the cessation of bile flow after 4 days. From the present study, it appears that such an impaired liver can continue at a reduced level of efficiency to sustain life for many additional days.

Comparisons are evident between the present results and those obtained by Simonsen and Dempster with homotransplantation of the kidney. Survival times were somewhat longer with the liver, since mean survival with kidneys was 4 days. Kidney transplants exhibit an immediate gradual functional deterioration with a rising blood urea nitrogen from the first day. The liver appeared to function normally for about 4 days, but its subsequent deterioration was similarly gradual. Evidence was presented by Dempster that the terminal event in the kidney was small vessel spasm with consequent inability of the organ to transmit blood, a general concept of rejection that has been strengthened by Edgerton's observations with skin grafts. Conceivably, a similar mechanism in the liver accounted, by means of splanchnic pooling, for the late gastrointestinal hemorrhages and mucosal sloughing seen in some dogs in the present study. At autopsy, both the kidney and liver homografts were abnormally large, pale, and firm.

Histologic findings were also comparable in many respects. In the kidney, cortical changes were dominant with early perivascular and periglomerular infiltrates, and later with edema, hemorrhage, more marked cellular infiltration, and structural disorganization. In the liver, aggregates of plasma cells and lymphocytes centered principally around the intraparenchymal portal triads, but the major parenchymal loss was frequently around the central veins. The ultimate degree of architectural loss was generally greater in the livers.

The precise mechanism of homograft rejection is not known. As a result of the penetrating analyses of Medawar (10, 11), the theory of acquired immunity has become a widely accepted explanation. The theory holds that a homograft acts as an antigen to evoke an antibody response from the host which causes rejection of the graft and confers a permanent immunity to all tissues from the same donor. The interval between placement and rejection of the graft is accounted for as the time necessary for the antigenic substance to get to and mobilize a response from the antibody-forming centers. Algire has shown that invasion of the graft with host lymphocytes is necessary for rejection. The principal evidence that rejection is due to an acquired host immunity was the demonstration by Medawar (10) that a second graft from the same donor is rejected in an accelerated fashion.

In the present study, the fate of the liver homograft has been shown to be comparable to other transplanted organs or free grafts in that it is ultimately rejected by the host. The converse, namely an effort of the graft's antibody mechanism to kill the host, has been the subject of lively interest since Simonsen and Dempster suggested the possibility with kidney transplants. Both Billingham and Brent's "runt disease" and Trentin's "secondary homologous disease" are thought to result from the attack of mature homografts upon fetal and irradiated hosts respectively. In the case of the liver, which has been shown by Berg and others to constitute well over half, and perhaps more than 90 per cent, of the splenectomized dog's reticulo-

endothelial system, any reaction against the host would be expected to be magnified.

From a functional viewpoint, there was no consistent evidence that any of the host organ systems were seriously challenged by graft initiated cellular or humoral antibodies. Renal and hematopoietic functions were most reliably monitored. Urinary output was generally good, and rises in blood urea nitrogen occurred terminally in only 3 of 18 dogs. Postoperative granulocytic response, presumably of host bone marrow origin, was adequate and sometimes prodigious. Except for complications related to surgery, cardiac or pulmonary system deterioration did not occur.

Histologically, however, host organs known to possess reticuloendothelial elements were universally infiltrated with lymphocytes and especially plasma cells in the same general manner as the graft itself. In addition, active proliferation of fixed mesenchymal tissue in and around blood vessels was prominent, a finding which is also common in a rejecting graft. It would be tempting to regard these findings as evidence of a graft attack on recipient organs, especially since such multiorgan changes have not been noted after placement of smaller and less immunologically active homografts.

Admittedly, no definite conclusion can be reached, but certain evidence at the present time is against this concept. As noted previously, function of the host organ systems was not impaired. Secondly, if mononuclear cells were originating and migrating from the homograft to host tissues, one would expect a ubiquitous distribution. Instead, such cells were found only in those tissues which were themselves capable of a reticuloendothelial response. The recipient skeletal muscle, for example, had no infiltrate in any of the 18 animals. Finally, it has been shown by Bjornboe that prolonged and intense stimulation with various bacterial or protein antigens will cause a universal reticuloendothelial response, astonishingly similar to that described in the present study, and Kojima has shown the same thing with a pure lipid antigen. Consequently, at present it seems most reasonable to believe that the histologic changes in host organs predominantly represent an exuberant response to the massive antigenic stimulation of the liver homograft.

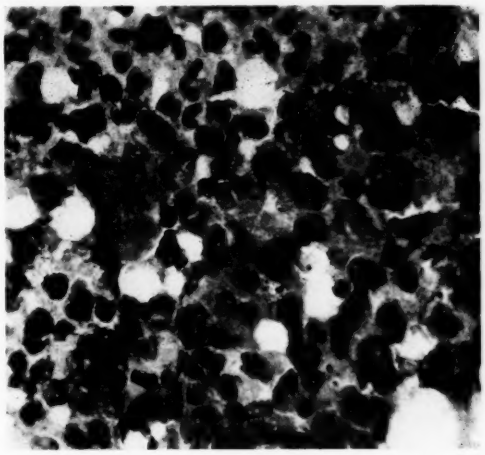


FIG. 16. Bone marrow in dog 65, after 20½ days. × 392. Note large numbers of plasma cells.

An alternative possibility is that the widespread alterations comprise a composite picture in which both graft versus host and host versus graft reactions have played a significant role. Studies in which either the liver graft or the host are rendered immunologically defenseless by irradiation should eventually clarify the issue.

SUMMARY

Dogs in which livers have been replaced with hepatic homografts usually die in 5 to 10 days. Liver metabolism is not detectably abnormal at first, but gradual deterioration of function commences on the fourth or fifth day.

There was histologic evidence of rejection in all dogs dying after 4 days. This ranged from minimal mononuclear infiltration to almost complete destruction of parenchyma. In the longest survivor, 20½ days, histologic changes were less profound than in many animals dying earlier.

Widespread histologic changes were found

in the host reticuloendothelial system, involving the bone marrow, kidneys, lungs, lymph nodes, and other tissues. These consisted of fixed tissue proliferation and infiltration of mononuclear cells, principally plasma cells. These changes were thought to be due to a general host reticuloendothelial response to the antigenic stimulus of the homograft.

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CONTRIBUTIONS OF ENDOSTEUM, CORTEX, AND SOFT TISSUES TO OSTEOGENESIS

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IN THE PAST CENTURY, the role of various tissues in osteogenesis has been the subject of many investigations. From these studies, several fundamental concepts have emerged. Adult, resting, fibrous periosteum is primarily a limiting membrane for bone and has little or no osteogenic capacity. The cambium layer of periosteum can be activated to produce new bone in the adult by trauma and certain disease processes. This osteogenic layer may be continuous with the lining of the haversian canals and the endosteum. Osteocytes of cortical bone, being trapped in their lacunae, do not participate in producing reactive, new bone. Reticular cells of the marrow, however, probably possess a capacity to produce bone when properly stimulated by their environment.

The role of paraspinal soft tissues in osteogenesis was demonstrated during previous studies by our group employing spinal fusions in dogs (7). The data suggested that diffusion of extracellular fluids from the muscle masses was important in promoting bone production. Sinee motion may have exerted an influence on the results, the present experiments were designed to eliminate this factor insofar as possible. In addition to reinforcing the findings of the spinal fusion study, present results are similar to those of other investigators and indicate that endosteal cells have a potent osteogenic capacity.

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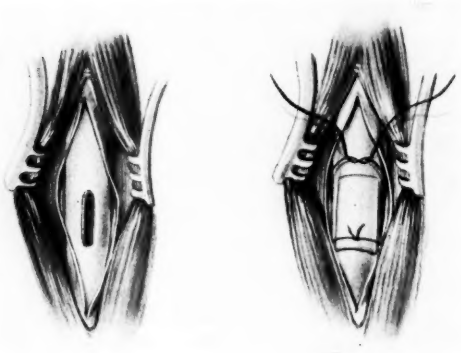
MATERIALS AND METHODS

Adult, mongrel dogs of both sexes, weighing 20 to 25 kilograms, were anesthetized with intravenous pentobarbital sodium, 30 milligrams per kilogram. The dorsal, midshaft regions of both radii were exposed. Fibrous periosteum was incised longitudinally, stripped from the cortex, and the cambium layer removed by light scraping. Two drill holes, measuring 0.4 centimeter in diameter, were made in the radii, one 2 centimeters proximal to the other. Saline and slow rates of drilling were used to minimize heating of the bone. The segment of bone between the two holes was removed with a sharp osteotome, so that a defect 0.4 centimeter wide by 2.0 centimeters in length resulted. The ends were semicylindrical in shape. This basic cortical defect (Fig. 1) was employed in each of the three experimental groups.

Group I consisted of 3 animals in which a defect in one radius was left untreated, while a defect in the opposite radius was covered with a 1 by 3 centimeter sheet of nylon reinforced HA millipore. The millipore sheet was anchored in position by 2 circumferential silk sutures passing around the shaft of the radius just proximal and distal to the defect. In 1 of these animals, trabecular, endosteal bone was curetted from the inner margins of the defect for a distance of approximately 5 millimeters.

Group II contained 5 animals in which the defect was isolated from the overlying soft tissue by an interposed millipore membrane on one radius. On the opposite radius, a 1 by 3 centimeter sheet of silicone rubber (silastic), 0.007 mil thick, was used to isolate



a b

FIG. 1. Scheme of the basic 0.4 by 2 centimeter cortical defect in extensor surface of midshaft of radius. This was left untreated or covered by a 1 by 3 centimeter sheet of millipore or silastic in groups I and II animals.

the soft parts from the cortical defect. In 3 of these animals, the endosteal surfaces were curetted for a distance of about 5 millimeters.

Group III included 9 animals in which a total of 18 radial defects were isolated from both endosteal and overlying soft tissue elements. This was accomplished by drilling a series of closely spaced, 2 millimeter holes through both cortices of the radius at right angles to the plane of the original drill holes.

TABLE I.—GROSS RESULTS AT 30 DAYS

Groups	*Animal Nos.*	*Endosteal curettage*	*Control*	*Millipore*	*Silastic*
	490	No	4	4	
I	599	No	4	4	
	728	Yes	3–4	3–4	
	473	No		4	4
	543	Yes		3–4	3–4
II	544	No		4	3–4
	589	Yes		3–4	3–4
	599	Yes		3–4	3–4
	504	No		3–4	2–3
	556	No		1*	2–3
	557	Yes		3	1
	566	No		1†	3
III	569	Yes		3	2
	582	Yes		3	2
	764	Yes		3–4	
	764	Yes		3	
	767	Yes		3	2
	772	Yes		3–4	2

4, Defect totally bridged by bone.
3, Defect totally bridged; bone at ends, soft, opaque tissue in center portions.
2, Defect totally bridged; bone and/or soft, opaque tissue at ends, translucent material in center portions.
1, No bridging, regeneration limited to ends of defect.
* A seroma was found overlying this specimen.
† Lateral and medial bars fractured.

Cortical bone between these holes was removed with a sharp osteotome, so that two narrow slots were created medially and laterally (Fig. 2). These extended 5 millimeters proximal and distal to the ends of the central defect. The two slots were oriented toward the dorsal surface of the radius, so that a plane passed between them was tangential to the inner or medullary borders of the central cortical defect. In the last 6 animals of this group, vestiges of endosteum were removed from the inner margins for a distance of 5 millimeters by curettage. A 3 centimeter wide sheet of millipore was threaded through the slots and the two ends were overlapped superficial to the defect (Fig. 2b). Two circumferential silk sutures passing through the slots just proximal and distal to the ends of the defects secured the plastic (Fig. 2c). A similar procedure was carried out on the opposite radius and, in the latter instance, a 3 centimeter wide sheet of the impermeable silastic was substituted for the semipermeable millipore.

Fibrous periosteum was not closed in any of these groups. An accurate reapproximation of the overlying extensor muscle mass, however, was achieved so that these soft tissues were placed in intimate contact with the plastic membranes. Postoperatively, animals were maintained in individual cages and were administered a diet of Purina dog chow.

All animals were sacrificed by administering intravenous pentobarbital sodium, approximately 30 days after operation. The entire segment of the radius containing defects and membranes was resected and fixed in 10 per cent neutral formalin. A cross section measuring 2 millimeters thick was removed from the center of each specimen and longitudinal sections 19 to 20 millimeters long were prepared from the residual proximal and distal segments of the defect and adjacent cortex. Specimens were decalcified in formic acid-sodium formate solution, sectioned, and stained with hematoxylin and eosin-phloxine B.

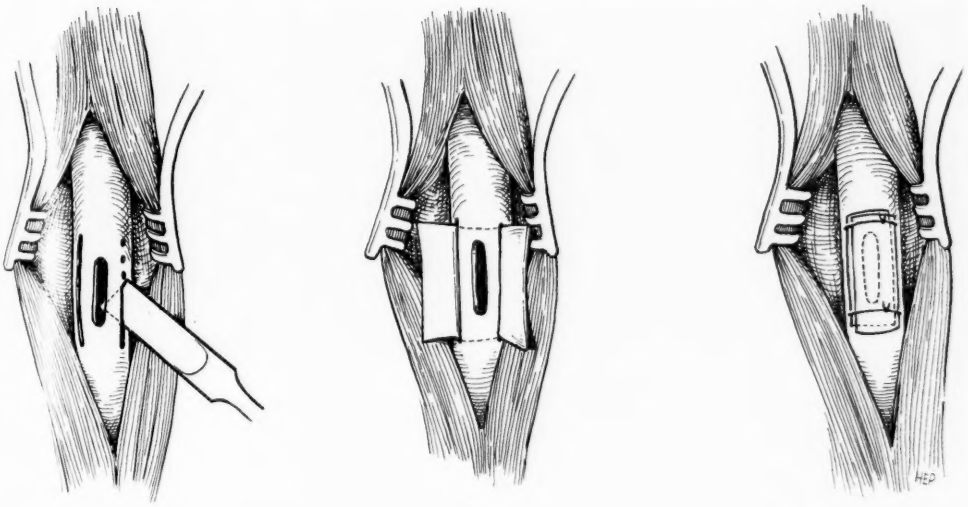


FIG. 2. Scheme for isolating the cortical defects in group III animals. a, Drill holes medial and lateral to defect are connected by removing intervening cortical bone with osteotome. b, Three centimeter wide strips of millipore or silastic are threaded through lateral and medial slots. c, Ends of membrane are overlapped superficial to defect and secured by circumferential silk suture running through slots proximal and distal to ends of defect.

RESULTS

Gross. Groups I and II.—The appearance of defects in all animals was essentially the same after 30 days. A mass of bony-hard tissue filled the area from which the cortical bone had been removed. The central portions of the regenerated areas were somewhat depressed below the level of the surrounding cortical margins. The overlying plastic membranes were found to be uniformly intact and were covered with a nonadherent, diaphanous veil of tissue which was part of the overlying soft tissues. The millipore and silastic were easily removed from the underlying regenerated tissue in the defect. In the 3 radii in which no plastics were used, muscle masses could not be separated easily from the tissues in the gap. The only evidence of bone formation in soft tissues outside the defects was found where the retracted edges of the longitudinally incised fibrous periosteum lay, medially and laterally.

Group III.—The description of the soft tissues, periosteum, and membranes just given for groups I and II animals applies equally well to this group. All membranes were intact and in place. Regenerating soft tissues had invaded the interval between the overlapping edges of millipore or silastic just superficial to the defects for a distance of only 1 to 2 millimeters.

Eight of 10 defects surrounded by millipore were bridged. Bony tissue was found throughout the gap in 1 specimen (No. 504). In the other 7 radii, a firm, white, opaque zone of tissue intervened between the bony zones which occupied the proximal 8 to 14 millimeters and distal 3 to 5 millimeters of the defect. Two animals did not heal in 30 days. A large seroma separated the soft tissues and millipore in one of the failures, while fractures across the bony bars medial and lateral to the cortical defect were found in the other. Serous fluid filled these two defects, in which bony regeneration was limited to the proximal 3 to 4 millimeters and distal 2 millimeters.

Silastic was used to wrap defects in 8 radii. The midportion of 7 defects contained

FIG. 3.

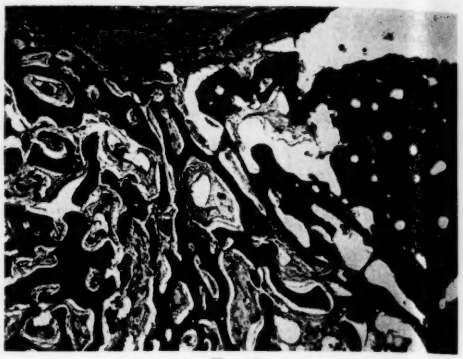


FIG. 4.

FIG. 3. Animal No. 504, fresh specimen from a group III animal, 30 days after operation. Millipore right and silastic left, removed to demonstrate differences in healing. Proximal portion of bone at top of photograph.

FIG. 4. Animal No. 544 (millipore). Center cross section, hematoxylin and eosin, ×23. Edge of cortical defect at right.

gelatinous, translucent, blood-tinged material which blended at the proximal and distal ends with 2 to 4 millimeters of bony or firm, opaque tissue (Fig. 3). This latter type, which appeared to be young, fibrous tissue, bridged the entire defect in the eighth specimen (No. 566). The gross results are summarized in Table I.

Microscopic. Tissue reactions to millipore and silastic were minimal. In most areas, a single layer of pseudosynovial cells separated regenerating fibrous connective tissue from the membranes. No foreign body giant cells were observed, except in areas where cotton fibers or other detritus had adhered to the plastics.

Groups I and II.—The histologic pattern of regeneration was essentially the same whether the defect had been left uncovered, or separated from soft tissues by millipore or silastic. The medullary canal beneath the defect was filled with numerous trabeculae of immature bone lined by active osteogenic cells. Few or no marrow elements were identified in this area. At the ends and sides of the defect, newly formed bone was continuous with the cortex but did not protrude beyond it. Cross sections taken through the center of specimens showed a mass of fibrous connective tissue and capillaries between the reactive medullary bone bridging the defect and the overlying millipore or silastic membranes (Fig. 4). At the interface between new bone and fibrous tissue, osteogenesis was active. With polarized light, collagen bundles were frequently observed linking osteoid with the area of loose fibrous tissue.

Cortical bone at the lateral and medial margins of the defects appeared relatively normal. Numerous lacunae contained nuclei. There was no evidence of an increase in the vascular bed or of perivascular new bone formation in the cortical bone. At the ends of the defects, however, few viable cellular elements remained in haversian canals or lacunae within 100 to 1,000 microns of the cut bone edges.

Regenerated areas at the margins of the defects appeared identical in animals whether endosteal curettage was carried out or not. A larger mass of loose connective tissue and more zones of active osteogenesis were found, however, in the central portions of

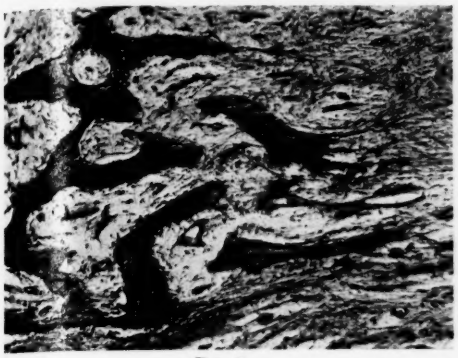


FIG. 5.

FIG. 5. Animal No. 557 (millipore). Longitudinal section of proximal portion defect, hematoxylin and eosin, ×63. These newly formed trabeculae were 1 centimeter from the proximal end of this defect, which is out of field to left.

FIG. 6. Animal No. 504 (millipore). Center cross section, hematoxylin and eosin, ×70. Few, if any, viable cells were found in the lateral cortical bar at the right of photograph. Gap obliterated by newly formed trabeculae.

FIG. 7. Animal No. 504 (silastic). Center cross section, hematoxylin and eosin, ×52. Compare with Figure 6. Scanty osteogenesis and loose fibrous tissue.

the gap in animals where attempts were made to remove endosteum. In some regions, a tongue-like projection of loose fibrous tissue extended into the middle of the medullary canal.

Group III.—The effects of curetting endosteal surfaces were clearly seen in this group. Despite attempts at thorough removal of endosteal elements, reactive new bone was found on the medullary side of the cortex within the silastic and millipore membranes in several animals. In these specimens, more reparative tissue filled the defects than in those in which examination of serial, longitudinal sections failed to disclose reactive, endosteal, new bone, There was no evidence that bone was formed on the periosteal surface of the cortex within the membranes in any animal. Outside the membranes, however, callus was found at the cut, retracted margins of the periosteum and the medullary canal was observed to be filled with newly formed, bony trabeculae.

FIG. 6.

FIG. 7.

Few viable, cellular elements were found in the haversian canals or lacunae within 100 to 500 microns of the proximal or distal cortical margins in most specimens. Three millipore and 1 of the silastic-protected specimens, however, did demonstrate numerous, normal appearing cells in the haversian canals and the cortical lacunae at both ends of the defects. In these, vascular canals were continuous between cortex and

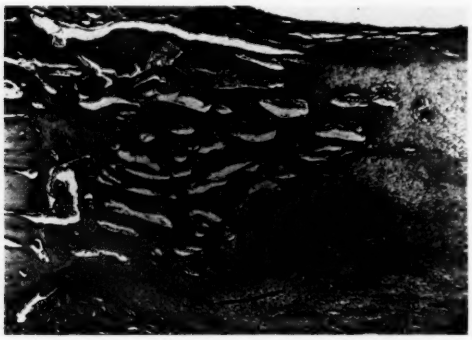


FIG. 8. Animal No. 556 (silastic). Longitudinal section, hematoxylin and eosin, ×21. Proximal edge of defect at left of photograph. Note continuity between haversian canal in cortex and vascular space of newly formed trabeculae. Cartilage is seen along interface between reactive bone and the relatively avascular fibrous tissue at right.

the reactive, trabecular bone in the gap. Viable, cortical bone was not found throughout the length of the bars of bone medial and lateral to the defect. In the center three-fourths of these bars, no vascular elements were found in canals and only an occasional pyknotic nucleus was observed in the lacunae.

Tissue, which appeared on gross observation to be bony, proved on microscopic examination to be largely reactive new bone, rich in young trabeculae and osteoblastic activity. The material described as firm and opaque proved to be a vascular fibrous tissue, while that characterized as soft and translucent was composed largely of a fibrin network supporting a few migrating, spindle-shaped cells and an occasional capillary. In the majority of specimens, regardless of the type of membrane used, the pattern of regeneration was often qualitatively the same, differences being merely of a quantitative nature. In all, there was more young bone in the proximal portion of the gap than the distal. The most mature trabeculae were found continuous with the cortex of the margins of the defect. Toward the center of the gap, trabeculae were sparser, oriented parallel to the long axis of the bone, and eventually disappeared as they blended with a loose, fibrous connective tissue (Fig. 5). This tissue in turn became less dense toward the more central portions. Capillaries were generally arranged parallel to the long axis of the defect in the areas of more mature tissue. A central, fibrin clot was found only in a few of the silastic-protected specimens. In 1 millipore-encased defect (No. 504), bony bridging had taken place across the entire gap (Fig. 6). Its silastic counterpart (No. 504) was bridged by bone only in the proximal 5 millimeters and distal 2 millimeters (Fig. 7). These specimens contained moderate amounts of endosteal new bone at the cortical margins inside the sheath. No evidence of cartilage or osteochondroid was found in any defect encased by millipore.

Cartilage was found in the proximal ends of two silastic-protected gaps. In these, residual, endosteal bone seemed to be responsible for a more extensive regeneration in the gap. Between the osseous trabeculae and the young fibrous tissue in the center of the gap, zones of chondroid material were frequently found (Fig. 8). Vessels were extremely rare in these zones and were practically nonexistent in the more distal fibrous tissue.

DISCUSSION

Adult dog radii proved well suited for this study. They were sufficiently large to permit removal of significant quantities of cortex without fracture. In addition, the only motor activity which may have affected regenerating tissue stemmed from action in the overlying muscle masses. The results indicate that the operative technique caused little bone necrosis except at the ends of the defects and the centers of the medial and lateral bars of animals with completely isolated defects. The finding of frequent acellular areas, where haversian systems had been transected, agrees with Ham's results. It should be emphasized, however, that 30 days after operation there were 4 specimens in which large numbers of viable, cellular elements were found next to the proximal

and distal margins of the defects. Since there was no evidence of remodeling in vascular canals in these 4, it is conceivable that cells survived the operative insult and may have migrated into the gap in the early phases of healing. If this were the case, it could partially explain the relatively large amount of new bone in defects where no residual endosteal elements or new, endosteal reactive bone is found. Recent tissue culture studies utilizing cortex, from which periosteal and endosteal elements have been stripped, show that the initial burst of cell migration takes place from transected vascular spaces within the substance of the cortex (1). These findings support, in part, the views of Lexer.

HA millipore was used in these studies because it is an inert, semipermeable membrane. While the pore diameter of 0.45 micron is sufficiently large to permit diffusion of fluids and macromolecules, it is too small to allow the passage of cells. Silastic, on the other hand, is an inert membrane, impermeable to cells and tissue fluids. This difference in permeability could easily explain why reactive bone was more abundant in defects isolated within millipore than within silastic. Cartilage was found, however, only in specimens surrounded by silastic and was intermediately placed between an area of young bone and relatively avascular connective tissue. In the 2 specimens bearing cartilage, abundant osteogenesis had probably resulted from residual endosteal elements within the silastic membranes. This result seems to reinforce those of the previous study of osteogenesis in canine spinal fusions where cartilage was frequently found beneath silastic. The data again suggest that there may be direct relation between a young "fibroblast's" nutritional status and the type of extracellular matrix produced by the cell.

Bloom, Bloom, and McLean, Enneking, DeBruyn and Kabisch, Williams, Lacroix, and others have demonstrated that endosteum is a rich source of osteogenic cells. As was expected, groups I and II animals, in which defects were exposed to the intramedullary canal, were more uniformly and completely filled by reactive bone at 30 days than those in group III. In addition, curettage of endosteum at the margins of the defect seemed to reduce the total amount of osteogenesis.

The results do not explain why regeneration was always more advanced at the proximal end of the isolated defects than at the distal. Similar observations have been made by Noback and associates in studies of neural regeneration. It may be possible that variations in hemodynamics in the vascular bed in different portions of the defect could be responsible, in part, for this finding.

One of the experimental techniques developed in this study may provide many advantages for further investigation of osteogenesis in vivo. The concept of physically separating periosteum and soft parts from areas of bone repair is certainly not new. Materials ranging from sheets of stainless steel to macerated, boiled rat femur have been used. However, we have not yet found previous reports of a technique for simultaneously isolating cortical defects from both endosteal and soft tissue elements. The use of millipore as the interposed membrane offers many advantages. As pointed out previously (2), it is inert and thereby probably does not involve cells, normally bent on osteogenesis, in a chronic inflammatory reaction. Since the material has a high flow rate, migrating cells that wander beyond their proliferating blood supply can still receive adequate amounts of nutrients by diffusion from tissues outside the membrane. We believe that a serial study of the sequence of events occurring in these isolated defects might be of great value. In addition, the technique may provide a more precise method for investigating the local effects of various agents on osteogenesis in vivo.

CONCLUSIONS

1. Endosteal cells play a critical role in osteogenesis and are probably responsible for a large portion of callus bridging defects

in adult, cortical bone. Osteogenic cells resident in haversian canal systems, however, seem to participate in the formation of new bone.

2. Healing was more rapid in defects isolated from soft tissue and endosteal elements by semipermeable millipore than in those isolated by impermeable silastic.

3. In the midshaft of canine radii, cortical defects isolated within millipore and silastic healed more rapidly at the proximal end than at the distal.

4. Soft tissues may play a role in the osseous healing of cortical defects by serving as a source of extracellular fluids to nurture cells.

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INTRADUCTAL PAPILLOMA OF THE BREAST

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INTRADUCTAL PAPILLOMA OF THE BREAST continues to present difficulties in diagnosis, therapy, and prognosis. Such lesions can be present with or without mass and with or without nipple discharge. They may be grossly visible or microscopic in size and benign or malignant. These contrasting possibilities have led to widely divergent views concerning the threat they present to the patient as well as their treatment.

A 51 year old white housewife was referred because for 1 month previously she had had a constant bloody discharge from both breasts. Papanicolaou smears had been taken from both breasts, and because one smear was class V she was admitted to the hospital. Since we could not determine from which breast the class V smear had come, as the slides had not been marked, and because we were unable to duplicate the finding in the previous report, Dr. Papanicolaou himself became interested and performed numerous stainings. His results were only class III from both breasts. Because of this and as there was no mass, a bilateral simple mastectomy was performed. Numerous sections from each breast showed intraductal papilloma and chronic fibrocystic disease. Because of the lack of invasion, the initial diagnosis was benign intraductal papilloma. Doctor Papanicolaou had some 400 slides made, and these were carefully reviewed by him, Dr. Fred Stewart and Dr. Arthur Purdy Stout, all of whom concluded that these represented carcinoma. The operation was performed in November 1954; the patient has been followed up for 5 years, and there is no clinical evidence of carcinoma at present.

Because of our experience with this patient and since we had long been interested in papillary papillomas of the breast, a more detailed study was made, and Drs. Stewart and Stout reviewed the sections in the cases reported.

Haagensen and associates reporting on 76 patients with intraductal papilloma of the breast treated by local excision, of whom all save 4 were followed up, found no patient in whom carcinoma of the breast developed. In their experience, only 1.3 per cent of carcinomas of the breast have been accompanied by serous or bloody nipple discharge. They believe that if careful palpation fails to reveal any tumor in the breast, it can be safely assumed that the patient with a bloody or serous discharge from the breast does not have carcinoma. These authors see no justification for the tendency of many surgeons to recommend simple mastectomy for intraductal papilloma. They say that many pathologists have difficulty in microscopically distinguishing benign papilloma from papillary carcinoma, tending to report a good many benign lesions as malignant.

This view is shared by Hendrick who followed up 208 patients for 5 to 18 years and found no greater likelihood that carcinoma of the breast would develop in patients with intraductal papilloma than in a like number of women in the same age group without this condition. In 2 of his patients, carcinoma developed in the opposite breast. He states that intraductal papilloma is a benign lesion and doubts if it ever becomes malignant.

Adair (1) in 1930 thought that benign papillary cysts and adenomas eventually developed into papillary cyst adenocarcinomas. However, by 1949 (2) his viewpoint had changed, and he wrote that this is not

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a precancerous lesion and will not undergo malignant degeneration. He states that it is benign and remains benign. Of cancer that causes bleeding from the nipple, he says that it began as cancer and did not develop from a previously benign papilloma.

Snyder and Chaffin, reporting 135 cases of papillary disease, found no case in which the patient died of carcinoma arising from the breast operated upon and in which an infiltrating carcinoma had not been found at the original procedure.

Madalin and co-workers reviewed 100 breasts removed from 85 patients by simple mastectomy because of discharge from the nipple. In this series they found intraductal papillomas in 58 and papillomatosis in 10. Of those in which a bloody discharge was noted, histologically 97 per cent contained intraductal papillomas or papillomatosis. They found a carcinoma in only 1 breast of the 100, and this patient also had proved carcinoma of the other breast. Their advice was, when there is discharge from the nipple as well as a mass, to excise the latter and act accordingly. In cases in which there is no mass, the offending duct should be locally excised, if possible; otherwise there should be a careful follow-up.

On the other hand, Kilgore and associates, in studying 190 patients with nipple discharge, found that, among 57 of these with intraductal papillomas and papillary cystadenomas removed locally, cancer developed in the same breast in 6 and in the opposite breast in 2. They believe that a woman more than 40 years old with bloody discharge or demonstrated papillary disease should be advised to consider simple mastectomy and that radical mastectomy be undertaken if cancer is found.

In reviewing 219 patients with nipple discharge, Donnelly found that 36, or 17 per cent, did not have a palpable mass. These 36 were operated upon and 30 showed definite signs of hyperplasia. Five had cancer and 6 showed precancerous lesions. He thinks that in a patient with a nipple discharge and no tumor, cancer has a 50 per cent chance of developing and he states that under these circumstances mastectomy is the treatment of choice.

Saphir and Parker group papillomas histologically into 3 types: fibrous, glandular, and transitional cell. The fibrous and glandular types do not recur. The last, or transitional type, is morphologically a benign tumor. It resembles a papilloma of the urinary bladder but may recur and look like cancer. For this lesion they advise a simple mastectomy.

In studying breast secretion smears, Papanicolaou and co-workers found that malignant cells can be distinguished from nonmalignant chiefly on the basis of nuclear abnormalities and other cytologic criteria of cancer. They believe that spontaneous nipple discharge should always be examined microscopically and state that, although the negative reports cannot be relied upon to exclude the presence of mammary carcinoma, the positive reports are as reliable in this as in any other application of the smear method.

CLINICAL CHARACTERISTICS

In the 125 patients studied at The New York Hospital (Table I), there have been 29 with gross intraductal papillomas of the breast and 96 with microscopic papillomas. With the exception of 3 males who had microscopic papillomas, all the patients were female. Patients with gross papillomas were more often postmenopausal, whereas those with microscopic papillomas were more often premenopausal. Race did not seem to make any particular difference. In the large majority of patients, gross papillomas occurred between the ages of 40 and 60, whereas the microscopic papillomas appeared in a somewhat younger age group, largely between the ages of 30 and 50.

The duration of symptoms varied (Table II). However, approximately one-half of the patients had symptoms lasting for less than 4 months, whereas there was an appreciable group that had symptoms lasting over 5 years. All the patients with gross

intraductal papilloma had a nipple discharge, whereas only 30 per cent of those with microscopic papillomas showed this symptom. The discharge was spontaneous in all patients with gross papillomas, and bloody in all except 2. Again, in the majority of those with microscopic papillomas, any discharge that appeared was spontaneous. However, almost one-half of these patients had a serous discharge. A palpable tumor was present in only 17 of the 29 with gross papillomas. In 91 of the 96 patients with microscopic papillomas there was a palpable tumor which was usually shown at operation to be chronic cystic mastitis. The lesion was located in the central portion of the breast in 27 of the 29 with gross tumor, 93 per cent, but in only 35 of the 96, 39 per cent, with the microscopic papillomas. Of 29 patients with gross papillomas, 6 showed retraction of the nipple and 5 had a history of pain. In 1 patient there was a history of inflammation. In contrast to this, only 1 patient with microscopic papilloma had a retraction of the nipple, whereas 24 had a history of pain.

TABLE I.—DISTRIBUTION, BY SEX, RACE, AND AGE OF INTRADUCTAL PAPILLOMAS OF THE BREAST IN 125 PATIENTS

	Gross	*Microscopic*
Patients	*29*	*96*
Sex		
Female	29	93
Premenopausal	12	69
Postmenopausal	17	24
Male	0	3
Race		
White	22	85
Colored	7	11
Age, yrs.		
10–19	0	3
20–29	1	14
30–39	2	24
40–49	10	38
50–59	10	11
60–69	4	4
70–79	2	2

TABLE II.—DURATION OF SYMPTOMS IN 125 PATIENTS WITH INTRADUCTAL PAPILLOMA OF THE BREAST

	Gross	*Microscopic*
Time	*29*	*96*
Under 1 month	5	24
1–4 months	10	34
5–8 months	4	6
9–12 months	1	1
1–5 years	6	16
Over 5 years	3	5
Unknown	0	10

PATHOLOGIC ANATOMIC CHARACTERISTICS

The clinical diagnosis of papilloma of the breast covers a variety of structural conditions. Of these, the two most frequently encountered are the large single or perhaps double or triple papillary tumors occurring in the ducts just beneath the nipple and causing a palpable mass, enlargement, and bloody discharge. The other is the diffuse and extremely multiple papillary proliferation of the epithelium in smaller ducts deep in the breast.

The large papilloma in the big ducts is usually covered by epithelial cells that are small and not markedly anaplastic or pleomorphic. The stroma is usually eosinophilic and hyaline. The whole appearance is that of a long-standing lesion. The small, multiple papillomas arise deep in the breast and have a different sort of epithelial covering. Here there is a much more impressive appearance of neoplasia. The epithelial cells are large, their nuclei vary in size and in shape, and there are occasional mitotic figures. The papillary growths are attached in many places to the walls of the ducts and, even though there is no demonstrable penetration of the basement membrane, there is the general appearance of malignancy.

Of this group of 125 patients operated upon for intraductal papillomas, carcinoma developed in 7 in the same breast, just under the scar of the previous operation or nearby. Two of these patients died of this disease. One died 3 years after operation at age 80, apparently without cancer. The other 4 are living without evidence of cancer 21, 18, 3, and 1 year after operation.

The eighth case, although originally diagnosed as a benign lesion, was later interpreted as malignant. These cases are reported in detail.

CASE REPORTS

CASE 1. A 55 year old white postmenopausal woman was first seen in 1934 because of a painless mass in the left breast of 4 weeks' duration. Examination revealed a hard, nontender 2 by 3 centimeter mass attached to the underlying tissue and 3 centimeters from the nipple. The skin was easily movable. Through a radial incision, the mass was found to consist of nodular solid tissue lying in breast parenchyma. This was excised and reported as fibrocystic disease with papillomas.

On readmission 19 months later, in 1935, the patient was found to have a mass that had been present for 3 months beneath the scar at the upper end of the incision. There was no discharge. A 6 centimeter infiltrating, firm mass with ill-defined borders and without retraction was found, excised, and reported to be duct carcinoma. A radical mastectomy was performed but no residual tumor was found. Radiation therapy was given.

Asymptomatic metastases developed 21 years later, in 1956, becoming symptomatic the following year. The patient declined hypophysectomy and was given radiation to the lumbar and pelvic regions. She died of metastatic carcinoma and a cerebrovascular accident in August 1958, 24 years after her original operation.

Pearce, Stewart, and Stout, who reviewed all of the slides in this study, interpreted the original sections as containing cancer.

CASE 2. A 33 year old white woman, 5½ months pregnant, was first seen in 1947 because of bleeding of 3 weeks' duration from the right nipple. Examination revealed a slightly tender, firm, freely movable, periareolar 1 centimeter mass without retraction of the nipple. Pressure caused a serosanguineous discharge from the nipple. Through a circumareolar incision, a freely movable nodule was removed, together with the associated duct, and reported as intraductal papilloma.

In 1949, 22 months after the original biopsy, she was readmitted because of a mass which had been present for 9 months. Examination revealed a movable, small, nontender mass 5 centimeters above the areola as well as a smaller mass beneath the superior portion of the right areola at the site of the old incision. A biopsy showed intraductal carcinoma. A radical mastectomy was performed and no axillary metastases were found. Sterilization by irradiation was attempted.

Four years later, in 1954, a 2 by 2 centimeter area in the right fourth rib was irradiated. In the succeeding years the patient underwent excision of residual carcinoma from the chest wall, bilateral oophorectomy, bilateral adrenalectomy, and hypophysectomy.

She died in February 1957, 10 years after the original biopsy. On review, all three pathologists called the original sections cancer.

CASE 3. A 72 year old white postmenopausal woman was seen in 1950 because of a persistent and spontaneous bloody discharge of 2 weeks' duration from the nipple of the left breast. Bleeding was activated on pressure, and assay of the material was reported as Papanicolaou class IV. Pressure on thickened cords radiating from the areola to the outer quadrants caused a spurt of blood. A medical circumareolar incision was made, dilated ducts were seen, and a segmental excision was performed. The pathologic report was chronic fibrocystic disease and intraductal papilloma.

Ten months later, in 1951, a second excision was made on the same breast for the same complaint, and intraductal papillomas were found. Eleven months later, in 1952, the procedure was repeated with a similar diagnosis. Four months later, at age 74, she extruded blood from the nipple as well as tissue that on microscopic section was interpreted as carcinoma. Directly above the left nipple was a firm, slightly tender, movable 3 centimeter mass. Pressure on this mass caused a discharge. Simple mastectomy was performed and revealed carcinoma.

Three years later, in 1955, a mass was noted under the scar; this was excised and reported as carcinoma. A radical mastectomy was performed but no residual tumor was found.

She died 3 years later, in 1958, at age 80 of heart disease, apparently without cancer.

All three pathologists interpreted the original sections as papilloma. One called the second specimen cancer and two called the third specimen cancer, while one said that this specimen was benign. All three agreed that the last specimen was carcinoma.

CASE 4. A 37 year old white premenopausal woman was first seen in 1936, complaining of a mass in the left breast and bloody discharge of 1 year's duration from the nipple. She had had repeated breast abscesses, but none in the last 18 months. In the lower inner quadrant of the left breast was a nodular, hard, movable mass 4 by 1.5 centimeters in size. In the lower outer quadrant of the same breast was another similar mass 4 by 1.5 centimeters in size. A thin, serosanguineous fluid could be expressed. A radial incision was made and both masses were excised. In one section there was a small papillary growth 6 millimeters in diameter reported as duct papilloma.

Four months after the initial biopsy she was readmitted because of a bloody discharge from the left nipple of 2 months' duration. There was a nodular, rounded 3 by 0.5 centimeter mass in the lower outer quadrant of the left breast near the nipple. Serous fluid could be expelled from the breast on pressure. A similar mass was present in the lower inner quadrant. Frozen section was reported as showing multiple intraductal papillomas. A simple mastectomy was performed and the tissue secured was reported as showing extensive malignant degeneration. Because

of this, 2 months later a radical mastectomy was performed. No cancer was found in the specimen.

Four years later, in 1940, she returned because of pain in the right breast. Because of nodularity in the breast, a biopsy was performed and reported to show marked chronic cystic mastitis with intraductal papilloma. A simple mastectomy was advised but never performed. She has been followed up for 21 years, to 1957, and there has been no recurrence.

On review, two of the pathologists called the original slides papilloma; the third said that the papilloma was benign, but that a separate nonpapillary carcinoma was present on one side of the papilloma. Two called the last section benign, while the third said that most of the ducts were benign but that there was carcinoma in one of the ducts.

CASE 5. A 43 year old white premenopausal woman was first seen in 1938 because of intermittent bloody discharge of 9 months' duration from her right breast. A few small, shotty, indefinite areas of nodularity were felt in the right breast. At operation, all the ducts were seen to contain dark fluid. An area of firm tissue was found and a 5 by 3 centimeter segment was removed. On microscopic section, multiple intraductal papillomas but no definite malignant changes were reported.

Three years later, in 1941, an irregular, movable, firm, nontender 4 by 4 by 2 centimeter mass was found in the upper inner quadrant of the right breast above the scar. There was no pain or bleeding from the nipple upon palpation. The breast was firm and had increased in size. Biopsy and frozen section revealed duct cell carcinoma. A radical mastectomy was performed, and axillary metastases were found in the specimen. After irradiation, she has been well without metastases for 18 years, to 1959.

On review, all three pathologists called the original sections carcinoma.

CASE 6. A 40 year old white premenopausal woman was first admitted in 1955 because of intermittent bleeding of 2 months' duration from the left nipple. There was no palpable mass. Pressure on the upper outer quadrant at the areolar cutaneous junction caused a reddish brown discharge from the nipple. Through a circumareolar incision in the upper outer quadrant of the breast, a "beefy red tumor" was seen in the duct and a segmental excision was carried out. This material was reported as showing chronic fibrocystic disease and no mention of the "tumor" was made.

Fifteen months later, in 1956, she was readmitted because of a palpable mass of 5 weeks' duration beneath the old incision. The nipple discharge had ceased. An irregular, firm, freely movable, slightly tender 2 by 2 centimeter mass was present in the upper outer quadrant adjacent to the nipple and under the scar of the previous operation. After biopsy, which showed cancer, a radical mastectomy was performed. Her 3 year follow-up has been uneventful.

On review, all three pathologists said that the original slides showed no cancer. The subsequent mass was beneath the previous scar, and on review all three called it carcinoma.

CASE 7. A 42 year old white premenopausal woman was first seen in 1957 because of a mass in the right breast of 4 months' duration. Examination revealed a freely movable, firm, rounded, 0.5 centimeter mass lateral and superior to the nipple. There was no nipple discharge or skin retraction. Upon excision, intraductal papilloma was demonstrated by microscopic examination.

There were no further complaints until 2 years later, in 1960, when two masses were noted: (1) At the upper end of the old incision was a firm, slightly irregular, movable 3 by 2 by 2 centimeter mass, attached deeply, which was nontender, painless, and unassociated with nipple discharge. (2) In the upper inner quadrant was a firm, round, freely movable 3 by 3 by 3 centimeter mass adjacent to the areola. Both of these were excised. The mass adjacent to the incision was chronic fibrocystic disease. The lesion in the upper inner quadrant was an intraductal carcinoma for which a radical mastectomy was performed. The mastectomy specimen did not contain tumor. Both sections were reviewed by only one pathologist.

The patient has continued well to date, although follow-up has extended only 1 year.

CASE 8. A 51 year old white postmenopausal woman was admitted in 1954 because of bleeding from both nipples of 1 month's duration. For the past 2 years there had been sporadic spontaneous yellow creamy discharge from both nipples. The breasts were symmetrical in size and shape. The nipples were everted. In the right breast thickened cords which radiated from the areola were felt, and brownish discharge was noted to come from the nipple. In the opposite breast, dark colored material drained from the nipple on pressure. No masses were felt.

One Papanicolaou class V specimen had been obtained before admission and multiple class II and III smears were obtained after admission but the class V could not be repeated. As it was not known from which side this smear had been obtained, bilateral simple mastectomies were performed.

The pathologic report was bilateral intraductal adenomatosis and chronic fibrocystic disease. Papanicolaou had many slides made and, after careful review, believed that carcinoma was present. The three pathologists concurred.

Five years later, in 1959, there was no evidence of cancer.

SUMMARY

There is a wide discrepancy in views expressed in the literature concerning the

malignant potential of intraductal papillomas.

The cases of 125 patients treated at The New York Hospital have been reviewed.

Eight patients who had been previously diagnosed as having benign lesions were later found to have a malignant lesion in the same breast either under or near by the scar of the previous operation.

Although we think that carcinoma starts as carcinoma and not as a benign intraductal papilloma, it is sometimes extremely difficult to make the proper diagnosis, and such patients should be studied carefully and followed up closely.

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AN ESTIMATION OF THE NITROGEN REQUIREMENTS FOR EQUILIBRIUM IN BURNED PATIENTS

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THERE ARE TWO IMPORTANT ASPECTS in the management of third degree burns: (a) removal of dead tissue followed by skin cover and (b) systemic support of the patient so that he can withstand the insult of the wound and its care. The systemic changes vary in magnitude with the size of the injury. In small burns the body reserves are adequate, and a successful outcome may be expected with minimal supportive therapy. Major burns deplete the patient rapidly, and thus almost perfect supportive therapy is necessary.

Studies were planned to obtain, with a high degree of accuracy, the important metabolic requirements of burned patients in various phases of the postburn course.

METHODS

Clinical background. Only patients who met predetermined criteria were included in the study. The factors considered were the depth and extent of the burn and the age and sex of the patient. The extent of the burn was assessed by an index calculated from the third degree area plus one-quarter of the second degree area described previously (12). The patients selected had an index of 20 to 35 with at least 15 per cent of the body surface involved in third degree burns. Burns of this size cause a strong catabolic response, yet the patients have a maximum chance of survival. The patients were well nourished, healthy men between the ages of 18 and 33 years who were on active duty with the armed forces when the burns were incurred. Normal control subjects were also studied and were on active duty. They were chosen because of their willingness to co-operate.

Eleven patients were studied for four 10 day periods which began on postburn days 7, 30, 60, and 90. These periods were selected because previous experience in uninterrupted studies of the entire postburn course had shown them to be representative of distinct clinical phases. A 10 day period was used because of the rapidly changing metabolic state; longer periods might have overlapped more than one of these phases. The seventh postburn day was chosen to begin the study of the catabolic phase, because a constant intake can seldom be maintained earlier. The anabolic phase, period 2, usually begins about the thirtieth postburn day in patients who have a burn index of the magnitude selected for this study. Period 3, the sixtieth postburn day, represents the anabolic phase in the patient who has recently had all of his granulating areas grafted. Period 4, the ninetieth day, represents late convalescence in patients who still show marked depletion of nitrogen and fat. The normal controls were studied for one 10 day period. In addition to the 11 patients studied for the four periods, 4 patients selected for study, in whom overwhelming sepsis developed, died between postburn days 22 and 44.

The clinical management of the patients was standardized within the limits dictated by their clinical course. The burn wounds were treated by the exposure method when possible. When occlusive dressings were

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TABLE I.—CONSTITUENTS OF THE 7 FORMULAS

Ingredient (gm./m.²)	*1*	*2*	*3*	*4*	*5*	*6*	*7*
Lipomul	306	228	148	66	—	—	—
Dextri-maltose No. 1	586	534	463	393	319	238	155
Whole eggs	—	100	100	100	100	100	100
Dried whole milk	—	72	193	315	417	417	417
Dried skim milk	—	—	—	—	13	100	189

TABLE II.—NITROGEN, POTASSIUM, AND SODIUM CONTENT OF THE 7 FORMULAS CHEMICALLY DETERMINED

Element	*Unit*	*1*	*2*	*3*	*4*	*5*	*6*	*7*
N	gm./m²	1.0	5.0	10.3	14.0	18.5	25.4	28.8
K	mEq./m.²	27.0	50.0	83.0	121.0	154.0	194.0	232.0
Na	mEq./m.²	28.0	40.0	58.0	77.0	96.0	115.0	136.0

TABLE III.—NITROGEN INTAKE IN GRAMS PER SQUARE METER, PLAN I

Study day	*Patient and control*				
	30	*31*	*32*	*33*	*34*
1	1.0	1.0	1.0	1.0	1.0
2	5.0	14.0	10.3	18.5	10.3
3	10.3	10.3	14.0	25.4	5.0
4	18.5	5.0	25.4	5.0	18.5
5	14.0	25.4	14.0	10.3	28.8
6	25.4	14.0	5.0	25.4	25.4
7	14.0	25.4	18.5	14.0	14.0
8	25.4	28.8	25.4	28.8	25.4
9	28.8	18.5	28.8	14.0	14.0
10	1.0	1.0	1.0	1.0	1.0

TABLE IV.—NITROGEN INTAKE IN GRAMS PER SQUARE METER, PLAN II

Study day	*Patient and control*					
	Pair 1		*Pair 2*		*Pair 3*	
	35	*36*	*37*	*38*	*39*	*40*
1 to 5	5.0	18.5	10.3	25.4	14.0	28.8
6 to 10	18.5	5.0	25.4	10.3	28.8	14.0

used during study periods they were changed at 5 day intervals.

Gauze pads soaked in distilled water were used during the study periods in order to hasten the separation of crusts in the second degree areas and to aid in the liquefaction of the eschar. Distilled water is unphysiologic, but it was used because sodium balances were to be determined. In an effort to maintain similar wound characteristics, gauze impregnated with petrolatum was applied to the burned surface except for the dressing change immediately before and at the time of grafting, when gauze impregnated with chloromycetin ointment was used. Grafting was begun at the termination of period 2, the fortieth postburn day, and was completed by the beginning of period 3, the sixtieth postburn day, with the following exceptions: Two patients had small grafting procedures on their hands on the twentieth postburn day. In another 2 patients, approximately one-third of the granulating surface was grafted between the twentieth and thirtieth postburn days. With the exception of 1 patient who was ambulated on postburn day 55, bed rest was maintained until the end of period 3 when all of the patients were ambulated. No anesthetic agents or blood transfusions were administered during the study periods. The control subjects were hospitalized on the metabolic ward for the period of study and were allowed only limited activity.

Balance techniques. The total intake of each individual was determined on the basis of the body surface area in square meters derived from the nomograph of DuBois using the reported preburn weight of the patients and the admission weight of the controls. Each subject was given 3,500 total calories per square meter with fat constituting 30 per cent of the caloric intake. The seven formulas used were prepared in the metabolic kitchen. They consisted of varying amounts of dried whole milk, dried skim milk, whole eggs, dextri-maltose No. 1®, lipomul®, and a flavoring agent (Table I). A liquid intake with few ingredients was chosen since it has been found most practical for maintaining constant dietary control (8). It allowed the incorporation of a wide range of nitrogen intake while keeping the total calories constant. It was easy to administer and to analyze chemically.

The composition of the intake of the patients was calculated as the average of the chemical determinations of the lot of foods being served during the study period (Table II). If a day's intake was incomplete, the unconsumed portion was analyzed, and the final daily intake was the known quantity offered minus the rejected portion.

The formulas were served in 9 equal portions at 2 hour intervals from 8:00 a.m. through midnight. Each patient was given the following vitamins per day in capsule

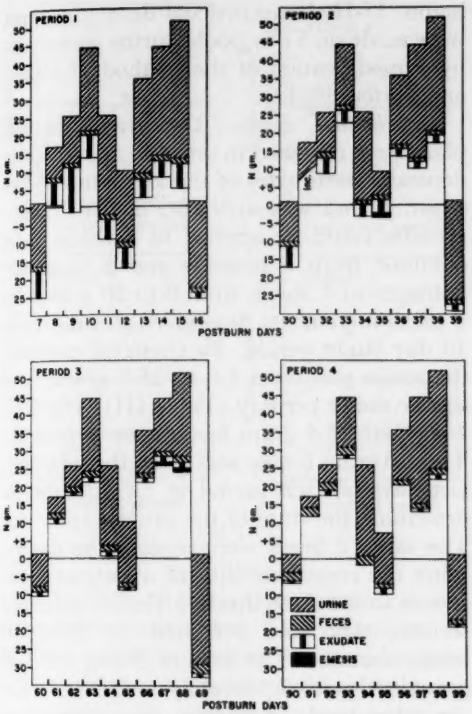

FIG. 1.

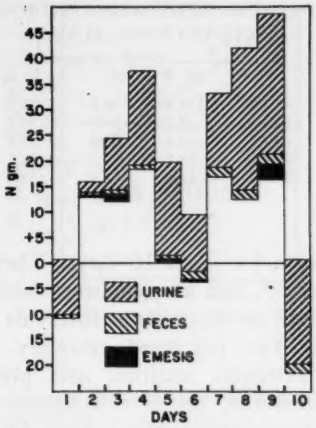

FIG. 2.

FIG. 1. Nitrogen balances of patient 32. The intake is measured up from the zero line and the output down from the intake line. The shaded area below the zero line shows negative balance, and the clear area above the zero line shows positive balance. Total intake and balance are shown.

FIG. 2. Nitrogen balances of control 32C. On the fifth and eighth days the intake was incomplete.

form: 1,000 milligrams of ascorbic acid; 6 milligrams of thiamine hydrochloride; 40 milligrams of riboflavin; 200 milligrams of nicotinamide; and 40 milligrams of calcium pantothenate. Water was allowed ad libitum. During period 1, in addition to the oral intake, all of the patients received 3 liters of 5 per cent glucose in water daily; and all but 2 patients received 75 to 100 milliequivalents of supplemental potassium acetate or potassium chloride intravenously.

Urine, feces, exudate, and emesis were analyzed for nitrogen, potassium, and sodium. The urine was pooled in 24 hour collections and refrigerated without added preservative. Carmine capsules were used to separate the fecal output for analysis as two 5 day collections, and the average daily output was calculated. The exudate losses were determined by extracting the accumulation in the dressings in a measured amount of water in a washing machine and analyzing aliquots of the wash water. The exudate losses in the dressings removed on the ward in the routine care of the patients were included in the output for the specific day. One-fifth of the exudate from the occlusive dressings removed at 5 day intervals during the study periods was allotted to the output of each day. Daily balances of nitrogen, potassium, and sodium were calculated by subtracting total output from total intake.

The exudate contribution to the total output of the burned patient is the most difficult to measure. A study was conducted to determine the per cent recovery of measured amounts of plasma from "clean" dressings, linens, and a combination of dressings and linens. After the addition of the plasma, the dressings were handled in a manner to simulate the usual handling of the dressings removed from the patients, that is, they were stored at room temperature for approximately 24 hours and in a

TABLE V.—TOTAL CUMULATIVE NITROGEN BALANCES IN GRAMS, PLAN I

	Patient and control				
Period	*30*	*31*	*32*	*33*	*34*
1	− 3.9*	−122.4	−49.1	− 78.7	− 67.9
2	+ 5.1	− 12.3	+14.1	+ 33.7	+ 40.5
3	+47.7	+ 63.4	+64.9	+ 79.4	+ 53.6
4	+87.1	+ 64.7	+75.2	+115.1	+ 82.7
Controls	+91.0	+ 44.4	+52.3	+133.5	+130.2

*Six days.

refrigerator for 7 to 10 days. They were then washed, and aliquots were withdrawn for analysis at 10 minute intervals for 70 minutes. The per cent recovery of the plasma nitrogen, sodium, and potassium increased during the first 40 minutes, after which time additional washing had little effect. The average recovery from the 3 types of specimen was 85 to 90 per cent of the amount added. Other specimens were inoculated with Pseudomonas aeruginosa and incubated for 7 days. There was no significant difference in the per cent recovery of nitrogen from these specimens.

The patients were weighed at the same time each day after voiding and before the first feeding. The weighing was accomplished on a scale accurate to 0.1 kilogram, which had a special attachment to accommodate patients on Stryker frames.

Blood was drawn for chemistry and hematologic studies while the patient was in a fasting state at the beginning and end of each study period. Each specimen was analyzed for sodium, potassium, chloride, carbon dioxide, nonprotein nitrogen, total protein, albumin, hemoglobin, hematocrit, and total eosinophils.

Standard procedures were used for the chemical analyses of all types of samples. Total nitrogen was determined by the micro-Kjeldahl method. Sodium and potassium were measured with a Baird flame photometer. The plasma was analyzed for chloride by the method of Schales and Schales, for carbon dioxide content by the method of Van Slyke, for nonprotein nitrogen by the method of Folin and Wu, and for total protein and albumin by the Kingsley biuret method as modified by Weichselbaum. 17-Hydroxycorticoid determinations were made on 5 day pooled urine specimens by a modification of the method of Silber and Porter (10, 13).

Experimental design. Two experimental plans were designed in order to arrive at independent estimates of the attributes of interest. Plan I was such that analysis of regression could be applied to balance data obtained from 5 patients and 5 controls. Nitrogen at 7 levels, from 0 to 30 grams in 5 gram increments, was given during each 10 day study period. By chemical analysis the range was from 1.0 to 28.8 grams per square meter per day (Table III). The 1.0, 14.0, and 25.4 gram levels were repeated. The 1.0 gram intake was given the first and last days of each period in an attempt to determine the state of the protein reserves. The other 2 levels were repeated to determine the reproducibility of a patient's response to the same intake given on nonconsecutive days and preceded by different levels of intake. The days of giving the 1.0 gram level were deliberately designated, but the other levels of nitrogen were randomized among the remaining 8 days of the study periods so that each patient received the levels in a different sequence. During each period the total intake per square meter was the same for each individual. The homogeneity of the response of the group to the intake was estimated by an analysis of variance of the cumulative balances. The effect of the preceding day's intake was assessed by an analysis of covariance. The intake of the previous day was the first variate, and the balance of the current day was the second variate assessed.

The best-fitting regression lines of the daily balances on the intakes were calculated by the method of least squares for the 4 periods of each patient and for the 1 period of each control. The data of the 5 patients were combined for each period, and the average balances on any given intake were corrected for the regression due to the effect of the previous day's intake by an extension of the analysis of covariance. Re-

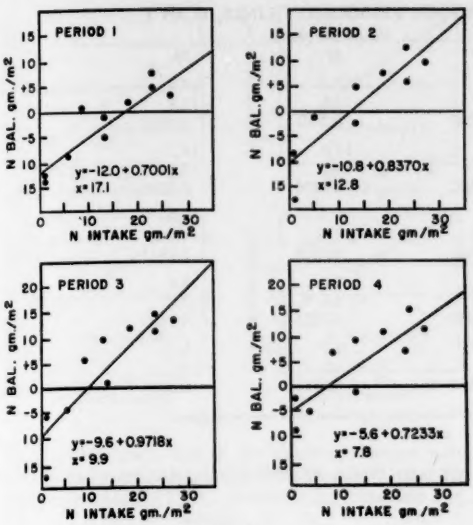

FIG. 3.

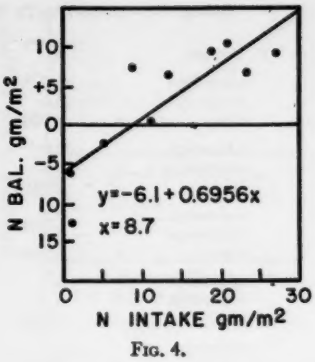

FIG. 4.

FIG. 3. Nitrogen regression lines of patient 32. The lines are significantly linear and that of period 3 is also significantly curvilinear.

FIG. 4. Nitrogen regression line of control 32C. The line is significantly linear.

gression lines of the adjusted balances on intakes were calculated. This treatment of the data made it possible to determine the level of intake at which equilibrium could be achieved, the maximum amount of storage possible with the given levels of intake, the efficiency of utilization, and obligatory loss on zero intake for the individuals and the group in each period of the study.

In plan II a cross-over experimental design was used to eliminate the effect of the normal decrease in nitrogen loss on a specific level of nitrogen intake during the postburn course (Table IV). The same levels of nitrogen used in plan I, with the exception of the 1.0 gram level, were given to 3 pairs of patients and 3 pairs of controls. One member of each pair received a constant lower level for the first 5 days and a constant higher level for the last 5 days of each 10 day period. His partner received the higher level for the first 5 days and the lower level for the last 5. There was an increment of about 15 grams of nitrogen between the low and high levels of intake for each pair.

An analysis of variance of the balance data for the 4 periods of each pair of patients and for the 1 period of each pair of controls showed the difference between the members of each pair, the levels given, and the member-level interaction. The average daily balance for each level was calculated from the data of the 2 members who were given that amount and fitted lines obtained for the regression of the average balances on the intakes. This method permitted the same estimations from these data as from those of plan I: the intake necessary for equilibrium, the maximum storage possible on the levels given, the efficiency of utilization, and the loss on zero intake.

In both plan I and plan II the patients and controls were randomly assigned to a specific order of intake. Each patient received the same plan of intake throughout the 4 study periods. Unless otherwise indicated, the intakes and balances are discussed on a per square meter basis.

RESULTS

Balance data, plan I. The nitrogen balance data of patient 32 and control 32C, plotted in the conventional manner (Figs. 1 and 2), are representative of the group.

The daily nitrogen balances of the patients and the controls were closely related

TABLE VI.—CONSTANTS OF THE NITROGEN REGRESSION LINES, PLAN I

Period	Constants	Patient and control 30	31	32	33	34
1	x-intercept	15.0	23.7	17.1	17.4	19.9
	y-intercept	−13.6	−16.3	−12.0	−15.8	−12.8
	slope	0.9068	0.6863	0.7001	0.9055	0.6434
2	x-intercept	13.0	15.3	12.8	10.7	11.2
	y-intercept	− 8.4	−10.8	−10.8	− 7.8	− 7.7
	slope	0.6515	0.7092	0.8370	0.7229	0.6912
3	x-intercept	9.2	8.3	9.9	6.0	10.4
	y-intercept	− 5.5	− 4.5	− 9.6	− 4.2	− 7.0
	slope	0.5980	0.5496	0.9718	0.6911	0.6787
4	x-intercept	6.5	9.3	7.8	3.8	7.3
	y-intercept	4.2	− 6.2	− 5.6	− 2.8	− 4.6
	slope	0.6525	0.6712	0.7233	0.7483	0.6213
Controls	x-intercept	6.5	9.3	8.7	5.2	5.8
	y-intercept	− 4.5	− 5.3	− 6.1	− 4.5	− 5.0
	slope	0.6954	0.5099	0.6956	0.8627	0.8619

Intake and balance were converted to intake and balance per square meter before the regression lines were calculated.

TABLE VII.—CONSTANTS OF REGRESSION LINES OF ADJUSTED NITROGEN BALANCES, PLAN I

Period	x-Intercept Constant	S.E.	t*	y-Intercept Constant	S.E.	t*	Slope Constant	SE	t*
1	20.7	0.1938	31.885‡	−12.8	0.3460	9.479‡	0.6176	0.0750	0.450
2	13.1	0.1365	20.853‡	− 8.7	0.2488	8.166‡	0.6654	0.0753	0.063
3	9.3	0.1250	9.152‡	− 6.1	0.2007	4.772†	0.6608	0.0756	0.032
4	7.0	0.2155	3.519	− 4.4	0.3069	2.422	0.6250	0.0752	0.042
Controls	6.8	0.3624	—	− 4.5	0.5104	—	0.6672	0.0723	—

*Comparisons were: periods 1 and 2, periods 2 and 3, periods 3 and 4, period 4 and controls.
†Significant at 1.0 per cent level.
‡Significant at 0.1 per cent level.

to the daily changes in the intake. During period 1 equilibrium was achieved in patient 32 on the second day of study with a total nitrogen intake of 17 grams (Fig. 1). Isolated days of positive balance were observed when the total intake was 35 grams or more, although this was not consistent. The cumulative 10 day nitrogen balances, however, were negative for all of the patients during period 1 (Table V). On the first and tenth days the balances of patient 32 showed good agreement. In the group as a whole, when the repeated levels of intake were offered for the second time, good agreement was noted between the balances in half the instances. Good or poor agreement did not seem to depend entirely upon the previous level of intake.

During periods 2, 3, and 4 the agreement between the balances on the days of repeated intake was somewhat better than during period 1. During these periods all of the patients were in positive cumulative balance except patient 31, period 2. The balances became increasingly positive with each successive period. In general, the pattern of balances for the 10 day period of the controls was the same as that of the patients during the last period (Figs. 1 and 2). The balance of control 30C was similar to that of his partner patient during period 4 (Table V), 2 controls had less positive balances, and 2 had more positive balances than the partner patients during period 4.

Statistical analysis and regression lines. The planned statistical techniques were applied to the data from each period of the patients and the 1 period of the controls. Analysis of variance performed on the cumulative nitrogen balances showed no statistically significant difference in the response among the members of the group to the total intake, irrespective of the order in which the levels were given. By an analysis of covariance the significance of the effect of the preceding day's intake was assessed on the

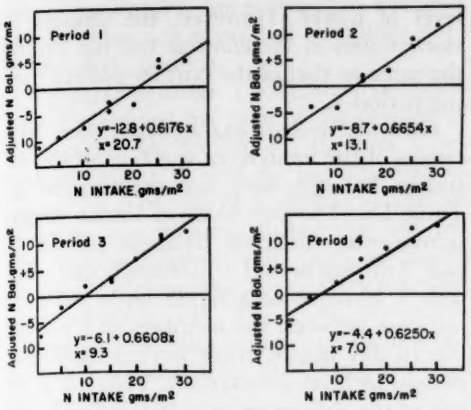

FIG. 5.

FIG. 5. Regression lines of the adjusted nitrogen balances of the patients in plan I. The combined balances of the 5 patients have been corrected for regression due to the effect of the previous intake. The lines are significantly linear.

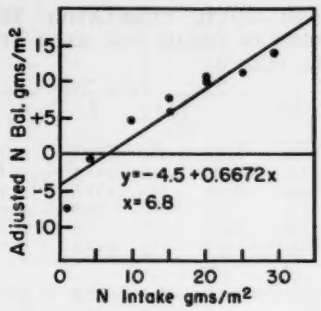

FIG. 6.

FIG. 6. Regression line of the adjusted nitrogen balances of the controls in plan I. The combined balances of the 5 controls have been corrected for regression due to the effect of the previous intake. The line is significantly linear.

combined data of the 5 patients for each period and of the 5 controls. The effect of the intake did not prove to be significant.

The best-fitting regression lines of the nitrogen balance on intake were calculated by the method of least squares, and the resultant regression lines of patient 32 and control 32C are shown in Figures 3 and 4.

The x-intercept, the point at which the regression line crosses the line of zero balance, theoretically represents the nitrogen intake required to achieve equilibrium. The theoretic requirements in grams per square meter for the individuals are shown in Table VI. All patients except patient 31, period 3, had a decreasing nitrogen requirement as the postburn course progressed, and by period 4 they were similar to the controls. The y-intercept, the theoretic nitrogen balance on a zero intake, diminished in a manner similar to the x-intercepts. The slopes of the regression lines, the change in balance with each gram change in intake, varied from period to period in each patient as well as among the patients; and no definite trend was discernible.

The combined daily balances of each patient period were corrected by the analysis of covariance for the effect of the level of the previous intake. Regression lines of the adjusted balances on intakes were calculated for each period (Figs. 5 and 6). These regression lines emphasized that the x-intercept and y-intercept decreased with the successive periods (Table VII). The x-intercept, y-intercept, and slope of the regression line from the combined control data were similar to those of the patients in period 4. A t-test of the x-intercepts and y-intercepts showed the differences between the values of the successive periods to be significant. However, the intercepts of the regression line of the controls were not significantly different from those of the patients during period 4. A t-test of the slopes showed no significant difference between periods.

The regression lines from the individual data were tested for curvilinearity by the orthogonal polynomial method of Fisher to determine which order equation best fitted the data. All the individual regression lines were significantly linear, and only patient 32 in period 3 and control 30C had regression lines that also were significantly curvilinear (Fig. 7). The regression lines of the combined data were similarly tested, and all of the lines were significantly linear.

Balance data, plan II. The nitrogen balance data of the pair of patients and controls who

TABLE VIII.—TOTAL CUMULATIVE NITROGEN BALANCES IN GRAMS FOR EACH LEVEL OF INTAKE, PLAN II

		Period				
Patient	*Intake*	*1*	*2*	*3*	*4*	*Controls*
Pair 1						
35	5.0	−119.4	−37.8	+14.5	+ 23.7	+ 4.7
	18.5	− 63.2	+13.4	+64.5	+ 74.1	+ 75.1
	Total	−182.6	−24.4	+79.0	+ 97.8	+ 79.8
36	18.5	− 29.8	−13.2	+68.9	+ 69.0	+ 58.2
	5.0	−103.3	−42.7	+ 1.6	− 13.1	− 1.6
	Total	−133.1	−55.9	+70.5	+ 55.9	+ 56.6
Pair 2						
37	10.3	− 88.8	−31.7	+19.5	+ 28.4	+ 11.8
	25.4	− 25.9	+35.9	+45.8	+ 83.0	+104.2
	Total	−114.7	+ 4.2	+65.3	+111.4	+116.0
38	25.4	− 12.8	+47.0	+85.1	+101.0	+ 65.1
	10.3	− 77.7	−21.7	−19.8	+ 14.7	+ 16.9
	Total	− 90.5	+25.3	+65.3	+115.7	+ 82.0
Pair 3						
39	14.0	− 27.7	+10.8	+44.2	+ 59.2	+ 60.7
	28.8	− 5.8	+35.2	+51.9	+ 79.7	+126.3
	Total	− 33.5	+46.0	+96.1	+138.9	+187.0
40	28.8	+ 43.3	+29.7	+57.9	+113.2	+ 97.1
	14.0	− 54.3	−24.2	+11.7	+ 31.1	+ 31.9
	Total	− 11.0	+ 5.5	+69.6	+144.3	+129.0

received the intermediate intake are shown in Figures 8, 9, 10, and 11.

During period 1 a cumulative negative nitrogen balance was present in all the patients (Table VIII). Patient 40, who received the highest intake given during the first 5 days, had a positive nitrogen balance during that time. All patients who received a daily nitrogen intake greater than 18.8 grams per square meter had a positive balance on isolated days.

During period 2 the 2 patients of pair 1 who received the lowest intakes were the only ones who had negative cumulative balances. All patients were in positive balance during periods 3 and 4, and the amount of storage in general reflected the intake. The controls had positive balances, and the degree of positivity reflected the level of intake. However, the amount of storage seen in the controls was not always the same as that of the partner patient during period 4.

Statistical analysis and regression lines. The results of the analysis of variance of the nitrogen balance data are summarized in Table IX. The two levels of intake caused significantly different balances except in pair 3 during period 3. Although there was only 1 instance of a significantly different response between the members of a pair to the 10 day intake, there were 3 significant patient by level interactions. This was a result of the difference in individual response to the order in which the nitrogen was given at the two levels.

Average balances for each level of intake were determined for the 4 patient periods and for the control period, and regression lines of the average balances on the intakes were calculated (Figs. 12 and 13). The values of the x-intercepts and y-intercepts decreased through period 3 and remained essentially unchanged during period 4 (Table X). The regression lines of patients and controls were significantly linear.

Plasma and whole blood determinations. Plasma concentrations of sodium, potassium, chloride, nonprotein nitrogen, total proteins, albumin, and globulin were determined at the beginning and at the end of each period, as were the hemoglobin, hematocrit, white cell count, and the total eosinophil counts. These determinations did not reveal any changes that could be attributed to the dietary intake. There was a moderate hyponatremia, anemia, and low serum albumin in periods 1 and 2. With the excep-

TABLE IX.—ANALYSIS OF VARIANCES OF NITROGEN BALANCES, PLAN II

	Pair 1			Pair 2			Pair 3		
Period	*Patient (order)*	*Level of intake*	*Interaction*	*Patient (order)*	*Level of intake*	*Interaction*	*Patient (order)*	*Level of intake*	*Interaction*
1	N.S.	25.61‡	N.S.	N.S.	11.94†	N.S.	N.S.	13.25†	6.01*
2	N.S.	13.49†	N.S.	N.S.	32.71‡	N.S.	N.S.	11.00†	N.S.
3	N.S.	38.39‡	N.S.	N.S.	28.87‡	9.76†	N.S.	N.S.	N.S.
4	4.60*	46.40‡	N.S.	N.S.	44.11‡	N.S.	N.S.	14.52†	5.91*
Controls	N.S.	96.31‡	N.S.	N.S.	28.02‡	N.S.	N.S.	27.45‡	N.S.

*Significant at 5.0 per cent level.
†Significant at 1.0 per cent level.
‡Significant at 0.1 per cent level.

tion of patient 39, the nonprotein nitrogen did not show any abnormal elevations during the study periods.

17-Hydroxycorticoids. 17-Hydroxycorticoids were determined for each of the periods of patients 31, 34, 35, 36, 37, the first 2 periods of patient 32, and the last 2 periods of patient 30. The rate of 17-hydroxycorticoid excretion was greatest during the first period and diminished with each successive period. This paralleled the urinary nitrogen excretion (Fig. 14). The excretion of 17-hydroxycorticoids remained somewhat greater than normal for this laboratory during period 4.

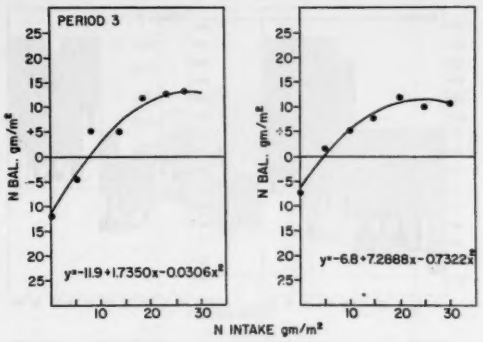

FIG. 7. Curvilinear regression lines of nitrogen balance of Patient 32, period 3, and control 30C. These were the only instances in which there was a significant curvilinearity in the regression of the nitrogen balances on intake.

DISCUSSION

Patient data. It has been generally accepted that nitrogen storage cannot be achieved consistently early in the catabolic phase. The finding of isolated days of positive balance on the days of high intake in plan I suggests that if a high level of intake can be maintained there would be a positive cumulative nitrogen balance. Such a balance was observed in patient 40 of plan II during the 5 day period in which he received the highest intake of the study. The absence of azotemia in this patient suggests that the retained nitrogen was stored as protoplasm. However, the desirability of attempting to cause a positive nitrogen balance by forced feedings in the more immediate postburn course is questionable, according to Hirshfeld and Levenson and their associates.

Nitrogen requirements for equilibrium as determined by plans I and II are summarized in Table XI. The requirements of plan II were higher during periods 1 and 2 than in the same periods of plan I. This is due to the difference in the experimental designs. The "zero" intake of plan I was not given in plan II, and the absence of this point influenced the value of the x-intercept. In addition, an average daily balance from 5 days on a given intake is less positive than a balance from 1 day on the same intake. In a study of the nitrogen utilization of protein depleted rats, Benditt and associates used two methods of approach similar to the two used in this study. As in this study, the results of their two plans showed an apparent difference in the requirements and utilization. They suggested that the difference was due in part to the fact that when the observation periods were short the "avidity of the tissues remained closer to maximal," whereas when the periods were longer the growth potential was significantly decreased toward the end of the period. It is possible that a similar phenomenon is observed in burned patients.

The data of the individual patients as well as the combined data of all patients in each plan indicated that the nitrogen requirements for equilibrium diminished as the postburn course progressed through convalescence. The factors which contribute to the larger requirements during periods 1 and 2 include the metabolic demands of the wound, the presence of infection, the degree of immobilization, and the losses via the exudate. During period 1 the patients were more febrile than during the subsequent periods. However, patient 33 who had a proved septicemia in this period showed no noticeable difference from the other patients in his response to the nitrogen intake. All of the patients had extensive

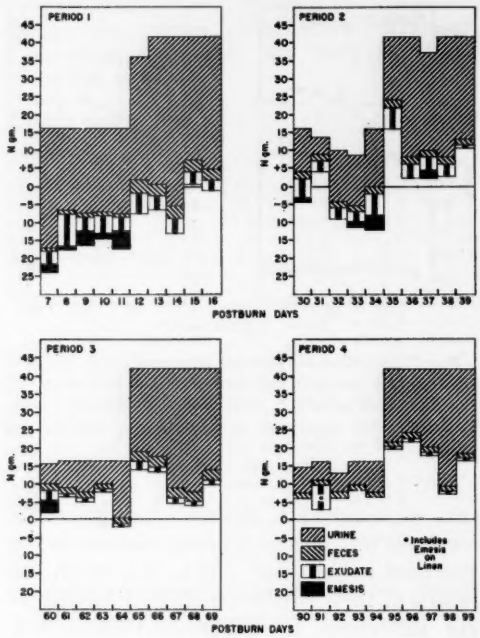

FIG. 8.

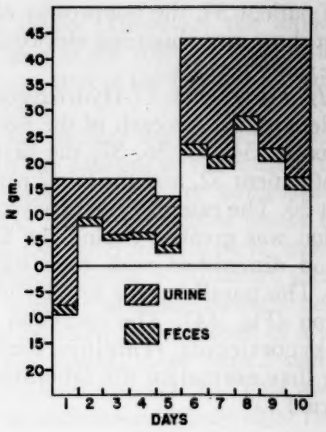

FIG. 9.

FIG. 8. Nitrogen balances of patient 37, pair 2. This patient was given a total daily intake of 16.0 grams for the first 5 days of each period and 41.8 grams for the last 5 days. During each period there were 1 or more days of incomplete intake. On the second day of period 4, emesis losses were recovered from the linen.

FIG. 9. Nitrogen balances of control 37C, pair 2. This control was given a total daily intake of 16.9 grams nitrogen during the first 5 days of the period and 44.2 grams during the last 5 days. On the fifth day the intake was incomplete.

granulating surfaces during period 2 which contributed to the magnitude of the nitrogen requirement. It was not until the interval between periods 2 and 3 that grafting was completed. This was reflected in the marked reduction of the nitrogen requirement during period 3. By period 4, when the wounds had essentially healed and the patients were moderately active, the nitrogen requirement was similar to that of control patients.

The role of immobilization is not clear. All of the patients remained immobile until the completion of period 3 except for patient 33. He was ambulated just prior to period 3, and his nitrogen requirement was considerably less than that of the other patients. The magnitude of adrenal activity is grossly indicated by the excretion of 17-hydroxycorticoids. The 17-hydroxycorticoids diminished as the postburn course progressed and, in general, paralleled the urinary nitrogen output.

The "zero" nitrogen intake given on the first and last days of each period in plan I was included in an attempt to measure the state of the nitrogen reserves. An individual with adequate stores reacts to a zero intake by releasing large quantities of nitrogen. A quantitatively similar negative balance would be expected on these days of "zero" intake if the nitrogen reserves were in a similar state. This was observed in the first 2 periods when the average negative balances on days 1 and 10 were 25.3 grams and 26.1 grams in period 1, and 17.9 grams and 18.6 grams in period 2. However, in the last 2 periods and for the controls evidence of repletion was seen, since the average negative balances on days 1 and 10 were 8.7 grams and 18.8 grams in period 3, 7.7 grams and 13.3 grams in period 4, and 4.9 and 8.2 grams for the controls.

The y-intercept, the negative balance on a zero nitrogen intake, represents the basic quantity of nitrogen necessary to maintain

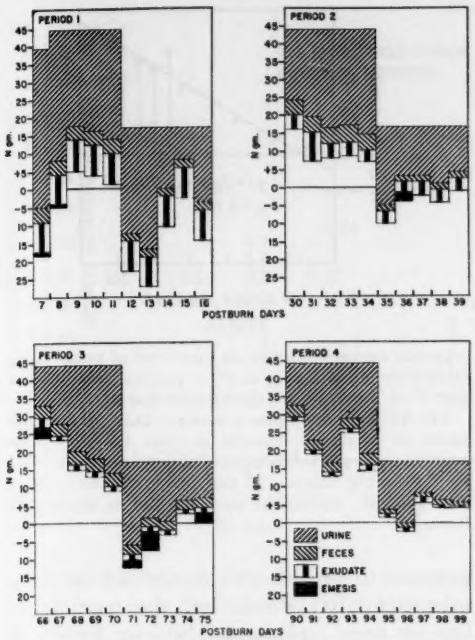

FIG. 10.

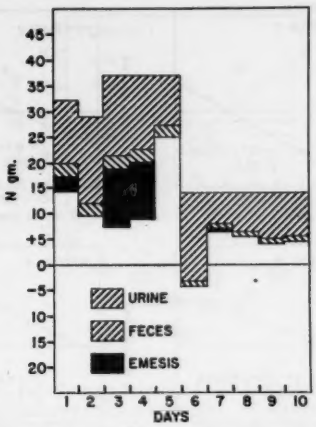

FIG. 11.

FIG. 10. Nitrogen balances of patient 38, pair 2. This patient was given a daily total of 44.2 grams nitrogen during the first 5 days of each period and 16.9 grams during the last 5 days. On the first day of period 1, the intake was incomplete.

FIG. 11. Nitrogen balances of control 38C, pair 2. This control was given a daily total of 37.2 grams nitrogen for the first 5 days of the period and 14.2 grams for the last 5 days. On the first and second days the intake was incomplete.

the body's metabolic processes. In the controls, this quantity is composed of the obligatory urinary nitrogen losses and the endogenous fecal output. In the patients, additional factors contributed to the larger values of the y-intercepts, such as the effects of infection and the exudate losses. As the postburn course progressed and the exudate and degree of febrility diminished, so did the values of the y-intercepts. By period 4 these values for the patients were the same as the controls.

The slope of the regression line describes the change in the balance with each change in intake. There was no significant difference between the slopes of the lines of the successive periods. This finding was contrary to the hypothesis that the utilization of nitrogen would become more efficient as the postburn course progressed, that is, that the nitrogen storage per gram increase in intake would be greater with each succeeding period. Thus, although the requirements for equilibrium and the obligatory losses progressively decreased, the relationship between these parameters remained essentially unaltered.

The nitrogen intake necessary to produce maximum storage was not given in this study since, with the 2 exceptions noted, the regression lines were significantly linear. A suggestion of curvilinearity, unsubstantiated statistically, was noted in plan II during periods 2, 3, and 4. The upper limit of nitrogen storage probably could be reached, but it seems impractical to administer greater amounts of nitrogen and calories than those given in this study. Hirshfeld and associates gave larger quantities of nitrogen to acutely burned patients and found that azotemia and dehydration developed in the patients. Only patient 39 showed a moderate increase in the plasma nonprotein nitrogen during the study periods, and this could not be attributed to renal disease. Mild glycosuria developed in several of the patients during period 1, and was not associated with an increase in urinary nitrogen.

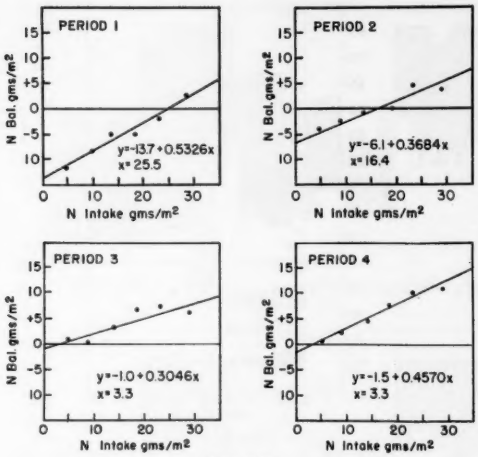

FIG. 12.

FIG. 12. Regression lines of average daily nitrogen balances on intake of the patients in plan II. The points represent average balances on each level of intake calculated from the balances of the 2 patients who received that level. The lines are significantly linear.

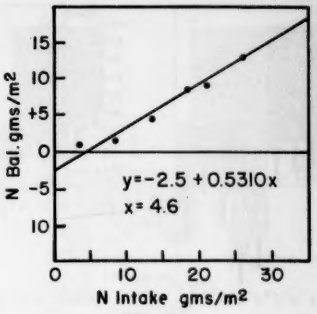

FIG. 13.

FIG. 13. Regression line of average daily nitrogen balances on intake of controls in plan II. The points represent average balances on each level of intake calculated from the balances of the 2 controls who received that amount. As can be seen, the line is significantly linear.

Four patients who were started on the study died between the twenty-second and forty-fourth postburn days. Study period 1 was completed in 3 of these patients. Inspection of the balances and regression lines of these patients did not show any remarkable departures from the data of the patients who received the identical intake and recovered (Fig. 15).

Severe hyperglycemia developed on postburn day 9, the second day of study, in the fourth patient who did not survive. He had a plasma glucose level of 1,200 milligrams per cent. The hyperglycemia was readily controlled with insulin, but the patient died 24 days later from a septicemia that apparently was not related in any way to the hyperglycemic episode. The hyperglycemia was not associated with acidosis. The occurrence of hyperglycemia in burned patients who had high caloric intakes was first reported by Evans and Butterfield. It appears to be related to carbohydrate intolerance after stress, but the mechanism has not been explained. The force feeding of burned patients should be carried out with caution and with a constant alertness for the manifestations of hyperglycemia. Subsequent to period 1 the levels of intake were tolerated without the appearance of hyperglycemia or other untoward sequelae. In fact, these patients appeared to regain a state of well-being and full range of activities earlier than like patients not force fed.

TABLE X.—CONSTANTS OF NITROGEN REGRESSION LINES OF COMBINED PATIENT DATA, PLAN II

Period	*x-Intercept*	*y-Intercept*	*Slope*
1	25.5	−13.7	0.5326
2	16.4	− 6.1	0.3684
3	3.3	− 1.0	0.3046
4	3.3	− 1.5	0.4570
Controls	4.6	− 2.5	0.5310

Control data. Eleven controls were included in this study in order to compare the response of the patients to the response of normal individuals. Previous experience (9) had suggested that late in convalescence the burned patient was able to store more nitrogen than a control who was given the same amount. However, this was not confirmed, since large and comparable amounts of nitrogen were stored by the patients during period 4 and by the controls. Furthermore, there was no statistically significant difference between the constants of the regression lines of the patients in period 4 and the controls (Table VII).

The protein intake recommended by the National Research Council for the normal

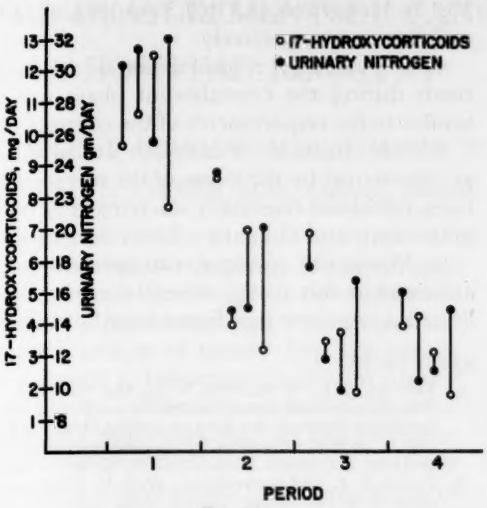

FIG. 14.

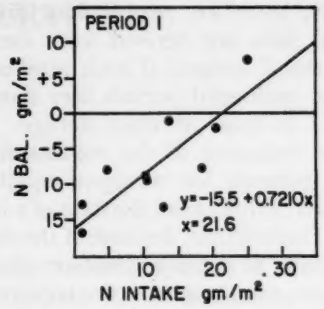

FIG. 15.

FIG. 14. Relation of urinary 17-hydroxycorticoid excretion to urinary nitrogen excretion. All determinations were made on 5 day pooled specimen. The normal range for this laboratory is 2.5 to 6.0 milligrams per day.

FIG. 15. Regression line of nitrogen balance on intake of a patient who had the same plan of intake as patient 31 (see Table VI) but died before period 2.

adult is 1.0 gram per kilogram of body weight per day. On this basis a 70 kilogram man with a surface area of 1.73 square meters should consume 6.5 grams of nitrogen per square meter per day. This is similar to the 6.8 grams and 7.0 grams per square meter requirement determined from the data of the controls and period 4 of the patients, in plan I of this study. The recommended allowance of the National Research Council for the normal person is generous because of a recognized variation in individual needs and variation in the nutritional value of proteins in mixed diets. It can be assumed that the recommended allowance is greater than the requirements for nitrogen equilibrium in a normal individual.

The nitrogen requirement for equilibrium of the controls as established by plan II was 4.6 grams per square meter per day. This is greater than the basic requirement of 2.4 grams determined by Hegsted who attempted to determine the basic requirements for nitrogen equilibrium in human adults by giving nitrogen at different levels and from different sources. He found that the nitrogen intake per square meter required for equilibrium was 2.9 grams when the nitrogen was from vegetable sources and 2.4 grams when an animal source of nitrogen was added to the diet. The discrepancy between these two studies is probably due to the difference in the experimental designs, the high calorie intake and the levels of nitrogen intake, and the sources of protein. Furthermore, no attempt was made to stabilize the controls of this study to a constant intake, since their data were to be compared with those of the patients in whom a stabilization period was impossible. As in plan I, the nitrogen requirements of the controls were similar to the nitrogen requirements of the patients during period 4.

As stated earlier, the requirements for equilibrium of the controls of both plans were higher than the basic requirements described in Hegsted's study and were more of the order of magnitude of the liberal National Research Council recommendations.

TABLE XI.—NITROGEN REQUIREMENTS FOR EQUILIBRIUM IN GRAMS PER SQUARE METER, PLANS I AND II

	Plan	
Period	*I*	*II*
1	20.7	25.5
2	13.1	16.4
3	9.3	3.3
4	7.0	3.3
Controls	6.8	4.6

We may, therefore, reason that, since the patients' data are derived from the same experimental designs, if such intakes were given for prolonged periods they should be sufficient to cause nitrogen storage.

These estimates of the requirements of burned patients for nitrogen equilibrium have been derived from the data of a limited group of individuals. Because of the deliberate selection of patients, postburn phases of study, and caloric intake, the requirements must be considered as tentative until further work has been done.

SUMMARY

1. The nitrogen requirements for equilibrium in burned patients were estimated by two plans of study in which the nitrogen intake ranged from 1.0 to 28.8 grams per square meter and the total calories remained constant at 3,500 per square meter. The two experimental designs were such that the balance data obtained could be subjected to regression analysis. Eleven male patients between the ages of 18 and 33 were studied for four 10 day periods. The periods represented the acute catabolic phase, the late catabolic phase, the anabolic phase, and the late convalescent phase. The patients studied had a burn index ranging from 20 to 35. Eleven normal controls were studied for a 10 day period.

2. Isolated days of positive nitrogen balance occurred on the days of high nitrogen intake during the acute catabolic phase. The cumulative nitrogen balance was positive in 9 of the 11 patients during the late catabolic phase and it became progressively more positive during the subsequent phases.

3. Regression analysis of the nitrogen balance on the nitrogen intake showed a progressive decrease in both the nitrogen requirements for equilibrium (x-intercept) and the obligatory nitrogen loss (y-intercept) as the postburn course progressed through convalescence. The amounts of nitrogen per square meter per day estimated to be necessary for equilibrium during the 4 phases ranged from 20.7 to 25.5 grams, 13.1 to 16.4 grams, 3.3 to 9.3 grams, and 3.3 to 7.0 grams, respectively.

4. The nitrogen requirements of the patients during the convalescent phase were similar to the requirements of the controls.

5. The efficiency of nitrogen utilization, as represented by the slopes of the regression lines, remained essentially unchanged as requirements and obligatory losses decreased.

6. Maximum nitrogen storage was not achieved in this study, since the regression lines did not show significant curvilinearity.

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THE MEASUREMENT OF CANCER SURVIVAL BY A HOSPITAL REGISTRY

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THE WIDESPREAD FORMATION of tumor registries has been stimulated by the realization that little is documented concerning the natural history of cancer and the results of attempts to influence the natural history by therapy. The American College of Surgeons lent its support to this endeavor and recommended that cancer activities include a registry unit (3). Three types of registries have developed as a result of specialized or co-operative needs: (1) the individual hospital registry; (2) the so-called central (city or state-wide) registry, as exists in certain cities and the states of Connecticut, California, Massachusetts, and Texas; and, more recently, (3) a "national" registry involving a selected number of central and individual registries throughout the country has been formed. Very little information has as yet been published from the hospital registry. It is our purpose to report some of these results and, perhaps more importantly, to discuss some of the limitations and methods of treatment of this type of data.

METHODS

This report represents the current registry information on cancer of selected sites accumulated between 1 January 1946 and 31 December 1955, with certain exceptions. The local purpose of the report is to provide the hospital staff with information on the classification and follow-up status of the cases followed up by the registry and, by so doing, to give the staff an over-all appraisal of its own work. Such reports suffer from many limitations, some of which will be pointed out. These limitations suggest the need for various improvements in the procedures for staging, for clinical classification, for the description of therapy, and for the summarization of charts. Such improvements substantially increase the value of these records to the clinician in his care of the patient and to the investigator in his evaluation of the over-all problem. A registry report that provides the type of information to be presented is not comparable to and serves a different function from reports developed from studies involving meticulous clinical evaluation and interpretation.

A report of this type has other limitations. The classification of patients, that is, the description of the disease in terms clear enough to be tabulated by registry staff, must be based upon the relatively diffuse and freely expressed descriptions provided in the patient's chart.

Attempt at classification by stage of disease is made from the chart by registry staff. The general form, modified appropriately for each site, is as follows: stage 1, in situ; stage 2, localized; stage 3, direct extension or regional spread; stage 4, distant metastases; stage 5, unknown. The problems of definition of and differentiation between stages necessarily vary somewhat from site to site. However, although considerable efforts were made to achieve accuracy in classification, our own experience and our consultation with others have convinced us that with existing records and for registry reports the borderlines between stages 1 and 2 and between stages 3 and 4 are difficult to define and give rise to many errors in

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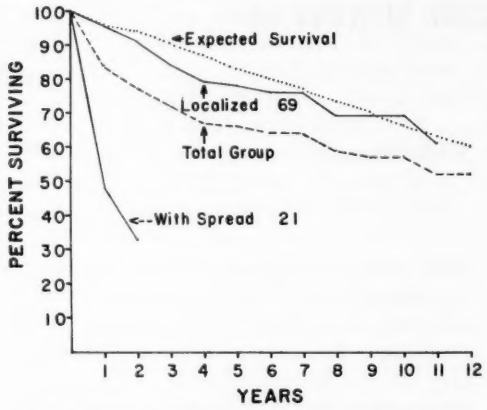

FIG. 1. Survival in 95 cases of carcinoma of the larynx —5 of unknown stage. Expected survival is calculated from life tables of the total population of the United States, including male and female and white and non-white groups. As can be seen, survival from the localized form of the disease does not depart very much from the expected survival.

classification. Therefore, only the pooled categories, "localized" (stages 1 and 2) and "with spread" (stages 3 and 4) are tabulated and graphed. Nevertheless, more detailed reports on the record from the physician and house staff would permit employment of the four stage classification. The classification "unknown" is used when the registry staff cannot evaluate the stage because of insufficient information. This inadequacy may result from an incomplete work-up or inadequate description of the findings. Certain groups of patients, such as those seen for consultation only, typically fall into this category. No attempt is made to classify the cancers by side in paired organs or by location within an organ, although we recognize that the location of the tumor often influences prognosis and choice of therapy. Such data are included in the registry abstracts and are available for more detailed studies. The conventions and policies used in classifying patients, although developed insofar as possible after discussion with interested staff members, are determined partly by the ability of the registry staff to use them with minimum risk of error. It is not always practical to seek consultation on individual cases, desirable though this would be.

Certain arbitrary decisions must be made in the classification of "initial therapy." Our basic categories include: surgery, radiation (roentgen-ray or radioisotope), chemotherapy, hormonal or hormone inhibitor, combinations of these, or no therapy at the University of Chicago (albeit possibly therapy elsewhere). In dealing with each site, only the more common forms of therapy and combinations are separated out. The remaining cases are for some sites included under "other therapy." Subdivision of these categories by type of surgery or by type and amount of radiation is yet another matter for more detailed study. One such example will be presented later. Whenever the chart indicates that exploratory surgery revealed an inoperable lesion, whether or not resection was carried out, the case is classified as "no therapy" if some form of palliative surgery was performed or not, despite the unknown influence of such procedure on survival. Alternatively, when the chart indicates that the type of surgery performed is tumor directed and performed with curative intent, the case is classified as

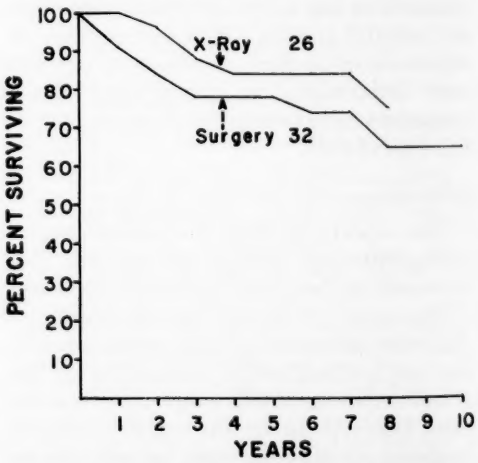

FIG. 2. Survival in 58 cases of localized stage of carcinoma of larynx. Comparison of survival of the two groups is rendered inaccurate in that smaller portions of each group, subsequent to the initial therapy, received the alternate form of treatment.

"surgical therapy." The problem of curative intent merits momentary digression. By this we mean that in the opinion of the surgeon he has extirpated the tumor. Our surgeons have been encouraged to commit themselves in this fashion in their operative reports. However, those cases are not reclassified which are shown by the surgical pathologist to have been instances of incomplete removal. It is often difficult to determine from the chart whether radiation treatment was given with curative or only palliative intent. Consequently, all such cases are placed in the category of "radiation therapy."

The decision as to what constitutes initial therapy is usually straightforward. Ordinarily, a regimen is prescribed and instituted within a short time after the diagnosis has been made. The plan of therapy is usually apparent from the first discharge summary, from consultations, or from notes on the early return visits. Difficult interpretations are often resolved by discussion with the attending physician.

CALCULATION OF SURVIVAL CURVES

In order to calculate survival curves certain technical issues must be resolved.

Dating of therapy. The calculation of survival by initial treatment subgroups should properly be dated from the time of initial treatment rather than from the time of diagnosis. In fact, the lapse between diagnosis at the University of Chicago Clinics and initial therapy averages considerably less than 1 month, and, therefore, we have dated all survivals from the time of first University of Chicago Clinics diagnosis.

Cause of death. It is sometimes thought worthwhile to separate deaths into two groups—those due to cancer and those due to other causes. The knowledge of precise cause of death, however, is so variable and unreliable it would be difficult to make reasonable comparisons between groups for specific causes of death. The analyses presented here are based on all deaths without consideration of cause.

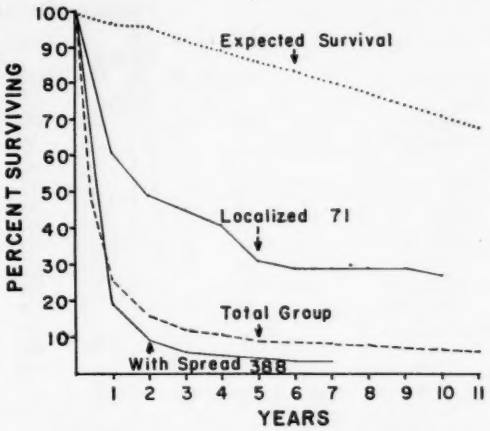

FIG. 3. Survival in 482 cases of carcinoma of lung—23 of unknown stage. Expected survival is calculated from life tables of the total population of the United States, including male and female and white and nonwhite. The poor experience in the total group is largely due to the disproportionate number of lesions of advanced stage compared to localized lesions encountered.

Multiple primary neoplasms. The registry maintains a separate abstract and calculates survival for each diagnosed site of primary cancer; a number of patients have had more than one such diagnosis. From some points of view it might seem desirable to classify each patient only under his first diagnosed primary cancer. However, if the first primary is one of the more common and less malignant cancers, such as skin cancer, such a procedure may seem inappropriate. No wholly satisfactory resolution of this problem is apparent, and in these reports a patient with several primary neoplasms is counted in each of the relevant sites. In some cases a patient may have diagnoses of 2 primary lesions referable to the same site, for example, in different portions of the colon, or in both lungs (i.e., separated in time and of different histologic type). Such patients are counted twice under the same site, but for most sites the number of such cases is believed to be statistically negligible. Among 499 patients with primary carcinoma of the lung, for example, 1 has 2 such diagnoses and thus 500 cancers are shown in the

TABLE I.—DISTRIBUTION OF DATA

	Larynx			Lung			Stomach			Colon			Rectum		
No. of cases	*Male*	*Female*	*Totals 95*	*Male*	*Female*	*Totals 500*	*Male*	*Female*	*Totals 447*	*Male*	*Female*	*Totals 491*	*Male*	*Female*	*Totals 320*
Race															
White	89	5		407	62		301	115		254	198		183	120	
Nonwhite	1	0		25	6		19	12		13	26		10	7	
Age, yrs.															
0–19	—	—		—	1		—	—		—	—		—	—	
20–29	1	—		1	5		2	4		3	2		1	2	
30–39	2	—		15	6		11	7		6	16		4	9	
40–49	11	1		54	10		33	13		28	35		23	23	
50–59	26	3		156	23		91	27		72	78		65	40	
60–69	39	1		171	16		126	46		102	64		63	42	
70 and over	11	—		35	7		57	30		56	29		37	11	
Stage of disease															
Local	66	3		60	17		34	19		123	104		93	66	
Under age 40			1			8			2			13			5
Over 40			68			69			51			214			154
With spread	19	2		351	49		273	105		137	115		88	53	
Under age 40			2			20			22			13			11
Over 40			19			380			356			239			130
Unknown	5	—		21	2		13	3		7	5		12	8	
Under age 40			—			—			—			1			—
Over 40			5			23			16			11			20
Deaths															
Here			9			172			131			101			47
Total			38			464			409			293			198
Autopsies															
Here			4			128			91			72			34
Total			7			153			99			83			49
Diagnoses at autopsy			0			18			7			9			1
Histologic proof of diagnosis (including autopsy)															
No.			95			418			380			470			310
Per cent			100			84			85			96			97

analysis. An additional 24 of these patients with primary lung cancer have had diagnoses of primary cancers of other sites and appear in the survival analyses for these sites as well.

Estimation of survival. The estimation of the proportion surviving a given number of years after diagnosis or treatment is complicated by the fact that the total group consists of cases diagnosed at varying times, including some diagnosed quite recently. In these circumstances there are a number of methods available for estimating survival. One such method, sometimes called the "reduced sample" method, consists in estimating the proportion surviving for T years (usually 5) by the ratio of the number surviving T years or more to the number diagnosed at least T years ago. This estimate of survival is commonly used and readily understood. However, it excludes more recent experience from the calculation, and it is sometimes criticized on that ground. Since the survival proportions at two different times are based on somewhat different groups of patients, the estimated proportion surviving 8 years, for example, may turn out to be somewhat less than the estimated proportion surviving 10 years. Although this phenomenon should cause no concern, it may tend to confuse the interpretation of survival curves. Finally, if individuals become lost from observation, corrections are needed which destroy the simplicity of the original estimate.

An alternative procedure consists in first estimating the conditional survival probabilities for each single year after diagnosis, and then estimating the proportion surviving for T years as the product of the separate conditional probabilities for each previous follow-up year. Corrections for

cases lost from observation are easily incorporated. For example, if 20 per cent are found to survive the first year, and, of those living and observable after the first year, 40 per cent survive the second year, then the estimated proportion surviving for 2 years is 40 per cent of 20 per cent, or 8 per cent. This procedure for estimating survival, as described by Berkson and Gage (4), is often called the "actuarial" method. No inconsistency of successive survival proportions can occur, and the complete follow-up experience for each individual is fully utilized. If, however, there has been a change in the survival probabilities, such as more favorable prognosis for the more recent cases due to improvements in therapy or a change in the type of case seen, the actuarial estimate may be seriously biased.

There are other alternative procedures and none can claim universal superiority. Since the actuarial method is by far the simplest to compute, we have used it.

For each site, survival curves are presented by classification of stage and by initial therapy for those subgroups including 10 or more cases, which tends to avoid presentation of curves in which the shape

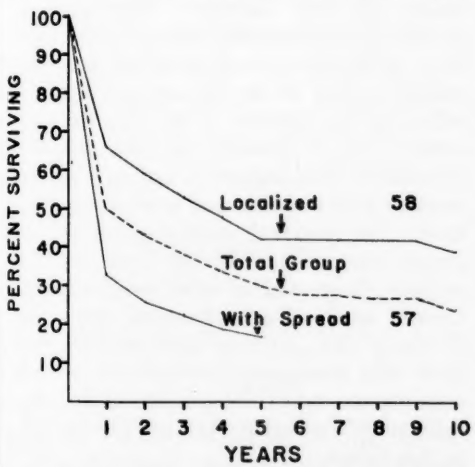

FIG. 4. Survival in 117 cases of surgically treated carcinoma of lung—2 of unknown stage. The experience of the total group here indicates that survival in cases of metastases found at thoracotomy is improved if resection is possible.

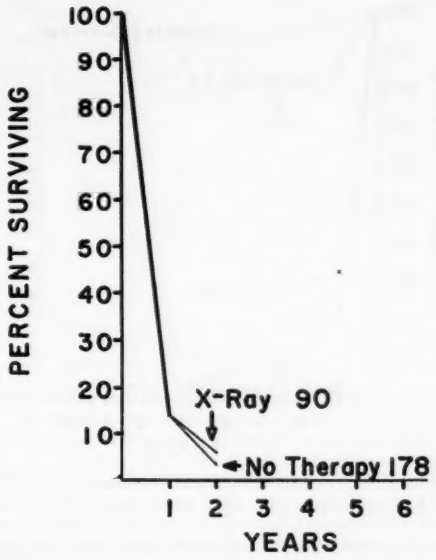

FIG. 5. Survival in 268 cases of carcinoma of the lung with metastases. The lack of any influence of roentgenotherapy upon survival in cases of metastasis is apparent.

is largely determined by chance variability. Likewise, each curve shown is truncated when fewer than 10 survivors remain. From these are abstracted the estimated proportion surviving 5 years (the usual five year survival rate), and the estimated time at which 50 per cent have died (the median survival time). Although the latter is a less familiar index, it has the advantage of being equally appropriate for conditions with long and short survival times. Since the median survival time is frequently short, it affords a more rapid measure of prognosis in evaluating comparative surgical techniques or the results of chemotherapy in special studies. The number of cases with incomplete follow-up in each category is given and, for those groups with more than 20 cases, the percentage with incomplete follow-up is shown as well.

"*Normal population*" *curves.* The normal population survival curve has been constructed from the 1949 to 1951 life tables published by the U. S. Department of Health, Education and Welfare and reported

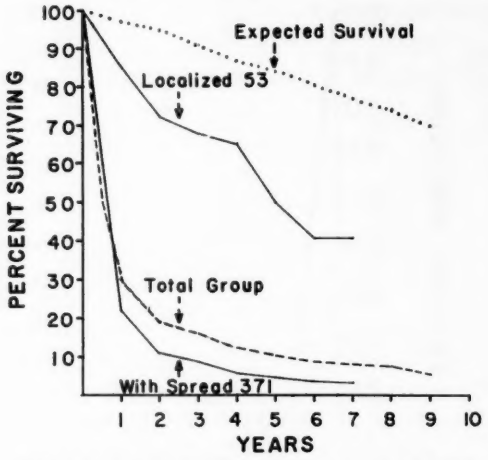

FIG. 6. Survival in 440 cases of carcinoma of stomach —16 of unknown stage. Expected survival is calculated from life tables of the total population of the United States, including male and female and white and nonwhite groups. The disparity in numbers of cases of localized and metastatic cancers once again significantly influences survival figure of the total group.

by Sirken and Carlson. The average age (to the nearest year) at the time of treatment of the cancer group was used as the starting point in calculating the age adjusted mortality rates for the general population. Survival by sex and race has not been analyzed in this report; thus, the life table for the "total population: United States, 1949-1951" was used. Included thereby in the curves of expected survival are male and female as well as white and nonwhite groups. As carried out by Dublin and associates as well as other investigators these curves provide a means of comparing mortality from cancer with the mortality of a large population of heterogeneous health status.

LIMITS OF INTERPRETATION

Although various curves and indices of survival are given, direct comparison of survivals in different categories is likely to be misleading. In part this limitation is inherent and well known: for example, the comparison between survivals of patients subjected to different treatments reflects the unavoidable selection of patients for each treatment, as well as the difference in treatment effects. The role of patient selection may be subtle and substantial. It is well recognized that associated medical conditions may contraindicate surgery, thus influencing the choice of therapy and the survival. Also, the apparent results of nonsurgical therapy may reflect the relatively unfavorable condition of the patients chosen quite independent of any specific anticancer effect of the treatment. It is usually difficult to assess in the record, and unless selection for treatment has been made by true randomization—a means of providing selection by chance—or its equivalent, the value of comparisons between treatments is limited. Selection may be warranted or necessary in cancer therapy, but it would be inappropriate to make conclusions as to therapeutic efficacy on the basis of comparisons of selected cases. The MacWhirter controversy concerning comparison of survival of patients with cancer of the breast treated by simple mastectomy and roentgen-rays, as performed in Edinburgh, and the classical, radical mastectomy performed in the United States, as described by Berkson and associates (5) and Lewison, illustrates the problem. Consequently, any analytic assessment of follow-up results should include a careful review of the nature and probable effects of the selection of patients for treatment made, if possible, by the attending physicians. The registry is not in a position to make such a review and none is attempted here. The survival curves presented are based on patients whose condition was initially diagnosed or who were originally treated at this institution. All other cases of cancer (i.e., patients with original diagnosis and treatment elsewhere or seen for consultation only) are handled in the same fashion by the registry but are not included in this report.

Representative sites and the form of presentation employed by the registry follow. Table I provides numerical information concerning items such as distribution by

race, sex, age, extent of disease, as well as autopsy information and numbers of cases with histologic proof of diagnosis.

SITES

Larynx. There were 95 cases of carcinoma of the larynx listed in the registry during the 10 year period 1 January 1946 to 31 December 1955. They constitute approximately 1 per cent of all cases of malignant neoplasm or a history of cancer seen during this period. The follow-up on these cases is 100 per cent complete. Lindsay and Ironside have shown that the anatomic location of the lesion may be of great importance in the prognosis, but our records are too incomplete to permit such a subclassification.

The outlook for patients with carcinoma of the larynx appears to be relatively favorable, as the estimated over-all 5 year survival is nearly 70 per cent (Fig. 1). Twelve years is, in this instance, an insufficient period to estimate the median survival time. As anticipated, the survival of patients with localized disease is considerably more favorable than of those with spread. The median survival for the group with spread is almost 1 year.

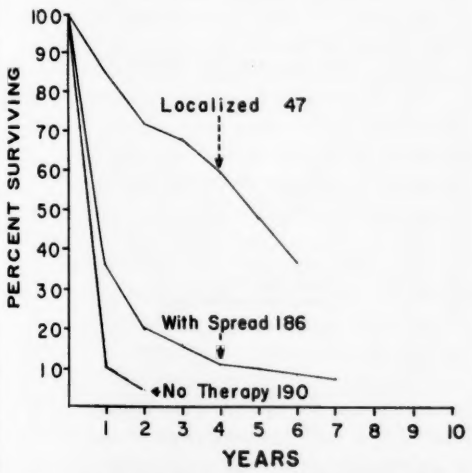

FIG. 7. Survival in 234 surgically treated cases of carcinoma of stomach—1 of unknown stage—and 190 in which no therapy was given. Survival of surgically treated patients with metastasis is close to that of patients receiving no therapy although a small fraction derive definite benefit. Such experience definitely reflects the readiness with which the surgeon undertakes resection in patients with metastasis.

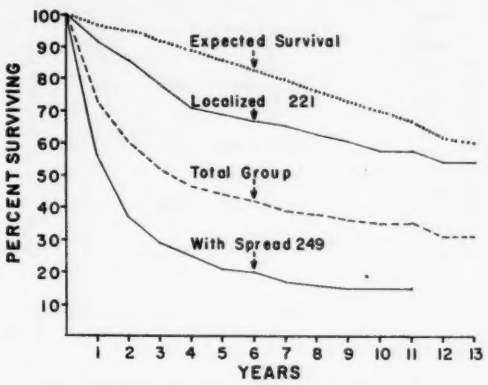

FIG. 8. Survival in 482 cases of carcinoma of colon—12 of unknown stage. Expected survival is calculated from life tables of the total population of the United States, including male and female and white and nonwhite. Survival in the localized group is gratifyingly close to the expected survival. The approximate midposition of the curve for survival experience of the total group reflects equality and size of the groups as well as the frequency with which definitive therapy is undertaken.

The major types of treatment of carcinoma of the larynx are surgical and roentgen-ray. Of the 95 cases reported, 32 patients received "surgery only" as initial therapy and 26 received "roentgen-ray only." Seven patients received combined surgical and roentgenotherapy, and 7 patients did not remain for treatment.

The comparison of survival of patients initially receiving surgery only and roentgenotherapy only (Fig. 2) is complicated by the fact that about one-fourth of those in the latter category subsequently were treated surgically. Roentgenotherapy may sometimes be preferred to surgery for localized lesions in order to preserve the voice, and the choice may be determined by whether or not cord fixation has occurred. In localized tumors treated by roentgenotherapy, surgery is performed later if the lesion persists or recurs. Thus, the comparison between "surgery only" and "roent-

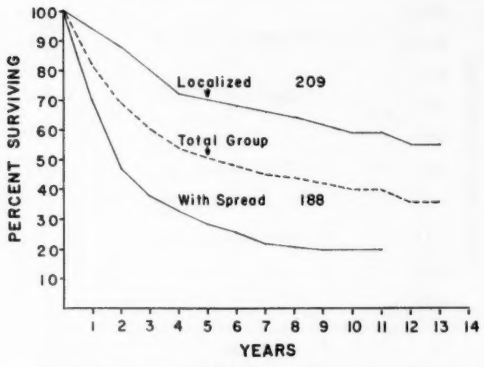

FIG. 9. Survival in 398 surgically treated cases of carcinoma of the colon—1 of unknown stage. The number of patients receiving surgical treatment is large and it is gratifying to note the number of them with a localized stage of the disease.

gen-ray only" is in fact a comparison of "surgery only" with "roentgen-ray only followed by surgery if and when indicated." Despite the possible effects of selection of patients for one or the other treatment it is, therefore, of interest to compare these two groups. There appears to be no striking difference in survival times between those initially treated by surgery and those initially treated by roentgen-rays.

Lung. The survival experience, during the 10 year period from 1 January 1946 to 31 December 1955 ranks with that of other highly specialized and skilled clinics in thoracic surgery (Figs. 3 and 4). Variations in survival presumably are due to the number of cases selected for curative surgery.

Definitive surgical therapy was deemed worthwhile and undertaken in only about one-fifth of the patients. Also, the curves of survival for any therapy except surgery seem almost identical to that for the group receiving no therapy (Fig. 5).

Stomach. There were 447 carcinomas of the stomach listed in the registry during the 10 year interval. They constitute almost 6 per cent of all patients with a cancer or a history of cancer seen at the Clinics during this period. In 7 patients the original diagnosis was made at autopsy, leaving 440 on whom survival calculations are based. The follow-up is complete on all but one.

Of the 440 cases originally diagnosed or treated here, surgical therapy was given in 234, 53 per cent. This includes subtotal and total gastrectomy and any more extensive surgery. Exploratory laparotomy only, bypass procedures, and other forms of noncurative surgery are not included. Sixteen patients received other treatments, e.g., surgery with postoperative roentgenotherapy, roentgenotherapy alone, and isotope, hormone, or chemotherapy. The remaining 190, 43 per cent, received no definitive therapy at the Clinics.

Survival times for patients with carcinoma of the stomach are short. The estimated over-all proportion surviving 5 or more years is 11 per cent, and the median survival time is only 0.5 year. The 5 year survival of the 53 with localized cancer was 50 per cent compared with 5 per cent for those with spread. The median survival times are 5.1 years and 0.4 year respectively. In 16 cases the documentation in the chart was incomplete and stage classification was impossible.

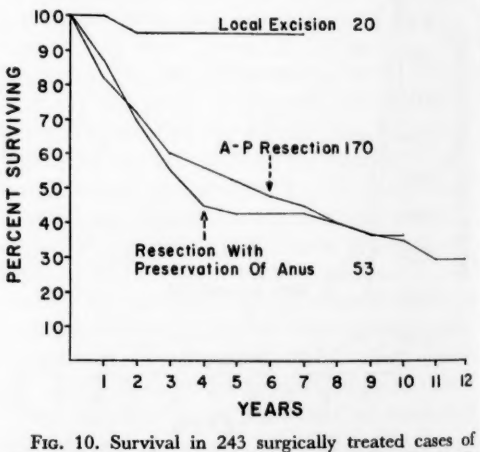

FIG. 10. Survival in 243 surgically treated cases of carcinoma of the rectum—all stages. The 1 death following local excision of a carcinoma of the rectum occurred in the second year and was due to myocardial infarction. While the curves of the other two modes of operation are surprisingly close for a long period of time, there is no doubt that selection of cases for the more conservative form is of crucial importance in the comparison.

None of these patients survived 5 years (Fig. 6).

Of the 53 cases classified as localized, surgical therapy was received in 47. In the remaining 6 cases no therapy was received here; in all except 1 surgical treatment was given elsewhere within 1 month. Of the 371 cases classified as "with spread," in 50 per cent (186) surgical therapy was also received. For the latter, the 5 year survival figure is 10 per cent, contrasted to 0 per cent for those with "other therapy" or "no therapy" (Fig. 7). In part, at least, the difference is due to selection of the more favorable cases for surgical therapy.

Colon. Four hundred and ninety-one cases of carcinoma of the colon were diagnosed or initially treated between 1 January 1946 and 31 December 1955. The prevalence is approximately equal to that of carcinoma of the stomach, namely, about 6 per cent of cases of cancer encountered, and is about 61 per cent of the combined group of 801 cases of carcinoma of the rectum and colon. Nine were diagnosed at autopsy, leaving 482 on which survival calculations are based. Follow-up is 99 per cent complete.

Eighty per cent of the patients (398) were subjected to operation, and this group was almost evenly divided between those with localized tumor and those with metastases. No attempt is made here to evaluate survival from cancer in various sites in the colon or to evaluate the effects of subsequent "second look" surgery.

Survival with the localized form of the disease is quite good. The 5 year survival is 69 per cent and, remarkably, the median survival is almost 12 years (Fig. 8). When spread of the carcinoma has occurred, the over-all 5 year survival is 22 per cent and median survival 1.3 years. The 5 year survival of patients subjected to operation is 70 per cent for localized lesions and 29 per cent for lesions that have spread. The median survivals are greater than 14 years and 1.7 years, respectively (Fig. 9).

Rectum. Figure 10 is of current interest and pertains to survival of patients with

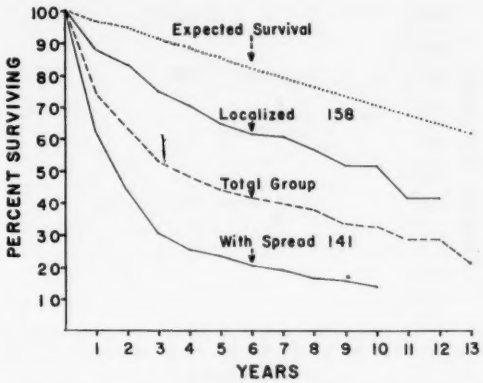

FIG. 11. Survival in the total group of 319 cases of carcinoma of the rectum—20 of unknown stage. Expected survival is calculated from life tables of the total population of the United States, including male and female and white and nonwhite groups. The approximate equality of the number of cases in these groups implies that early diagnosis is not occurring with the frequency one would hope for in a site so readily available.

carcinoma of the rectum treated by 3 different surgical techniques. While these are selected groups and comparison of the relative merits of one technique versus another would be misleading, it is of interest that when carcinoma in situ (or malignant adenoma) is excluded (1) local excision is an excellent treatment of certain polypoid rectal cancers, and (2) the median survival of those patients in whom the anus was preserved was 3.5 years and of those patients subjected to combined anterior-perineal resection was 5.5 years. Subsequent survivorship seems about the same with both groups, and after 7 years the survivorship is somewhat better for those patients upon whom abdominoperineal resection was performed. Of interest is the favorable (65 per cent) 5 year survival of 158 patients with localized rectal cancer, excluding carcinoma in situ (Fig. 11). Eighteen of this group either received therapy elsewhere or were untreated. Excluding this group, 69 per cent (140) enjoyed a 5 year survival (Fig. 12).

Childhood leukemia. In consideration of childhood leukemia, median survival is the better index. Of 23 patients encountered in 1947 and 1948, the median survival

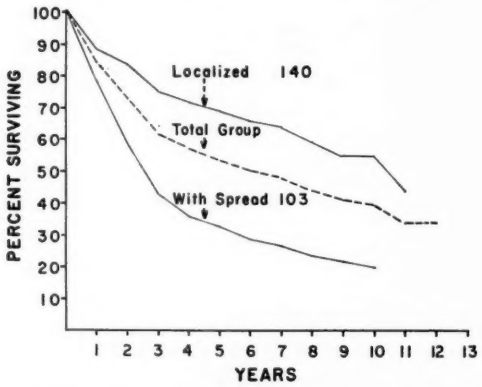

FIG. 12. Survival in 243 surgically treated cases of carcinoma of the rectum. We cannot explain why it was possible to treat surgically only two-thirds of the cases of carcinoma of the rectum while 80 per cent of cases of carcinoma of the colon were so treated.

was 3 months, while in 1957 and 1958 the median survival was 8 months. The maximum survival in the first period was 1 year as compared to 2 years in the second period. Here the difference may be found in improved chemotherapeutic agents combined with corticotrophin or adrenocorticosteroid therapy. Another similar example of marked improvement in survival is to be found in the chemotherapeutic control of choriocarcinoma.

SPECIAL STUDIES

Breast. This site provides an example of the more highly specialized type of service provided by the registry. The following data are part of the statistics developed by Allen and Rigler (1, 2) with the collaboration of the registry.

Two hundred and thirty patients received treatment for carcinoma of the breast between 1 January 1946 and 30 June 1951. Fourteen of these had bilateral primary breast carcinomas. Follow-up is 97 per cent complete. The over-all 5 year survival is 56 per cent, 77 per cent in those with localized lesions and 42 per cent in patients whose cancers had spread beyond the boundaries of the breast.

When one considers survival with respect to the various types of treatment, the 5 year survival rates are as follows: 63 per cent of those treated by radical mastectomy; 59 per cent of those treated by radical mastectomy plus roentgenotherapy; 54 per cent of those whose treatment consisted of simple mastectomy with or without roentgenotherapy; and, 17 per cent of those patients who had some other form of therapy, such as irradiation only, hormonal therapy, or sterilization. In a group of 198 patients selected by two criteria—first, absence of distant metastases and, second, treatment by radical mastectomy with or without roentgenotherapy—76 per cent of the patients with localized disease survived 5 years when subjected to mastectomy only, whereas 87 per cent survived when roentgenotherapy was added. Forty-eight per cent of patients with regional metastases survived 5 years after radical mastectomy only; 46 per cent when roentgenotherapy was added. The 5 year survival rate in this group as a whole was 60 per cent. These figures cannot be construed as being indicative of the effectiveness or ineffectiveness of roentgenotherapy, since the selection of patients for irradiation is not random, but rather is a function of many ill-defined variables.

The survival of the group of patients from 35 to 50 years of age conformed closely to the data reported by other authors (Table II). However, the small number of patients who were under 34 years of age did much better than is usually expected. And, the older age group also exhibited an unexpected tenacity. If one further divides those patients with lymph node metastases into groups determined by percentage of lymph nodes involved, it is seen again that with no axillary nodes, the 5 year survival rate is 77 per cent. If less than 20 per cent of nodes are involved, it is 63 per cent. When 20 to 50 per cent of the nodes contain tumor, the 5 year survival rate is 53 per cent. When over half of the lymph nodes are involved, the outlook drops to a 20 per cent 5 year survival (Table III).

Data were available as to the size of the tumor in 216 patients. With lesions of less than 2 centimeters, the prognosis was excellent (93 per cent 5 year survivorship). After the tumor had attained a diameter of 9 centimeters or greater, the outlook was much gloomier. Only 10 per cent of the group so designated survived the 5 year period (Table IV).

TABLE II.—INFLUENCE OF AGE OF PATIENT ON 5 YEAR SURVIVAL

Age group, yrs.	*Total No. of cases*	*No. alive after 5 years*	*Per cent alive after 5 years*
Under 34	12	10	83
35–39	20	11	55
40–49	62	34	55
50–59	83	43	52
60 and over	53	30	57

TABLE III.—INFLUENCE OF THE EXTENT OF LYMPH NODE INVOLVEMENT ON 5 YEAR SURVIVAL

Per cent of nodes involved	*Total No. of cases*	*No. alive after 5 years*	*Per cent alive after 5 years*
0	87	68	77
1–19	33	21	63
20–50	45	24	53
Over 50	49	10	20
Not coded	16		

TABLE IV.—INFLUENCE OF THE SIZE OF THE TUMOR ON 5 YEAR SURVIVAL, PATHOLOGIST'S MEASUREMENT

Size, mm.	*Total No. of cases*	*No. alive after 5 years*	*Per cent alive after 5 years*
0–19	13	12	93
20–49	116	72	61
50–89	68	32	47
Over 89	19	2	10
Not coded	14		

TABLE V.—INCIDENCE OF POLYPS ACCORDING TO AGE OF PATIENTS

Age in yrs. at first proctoscopic examination	*No. of patients*	*Patients with polyps*	
		No.	*Per cent*
0–10	27	1	3.7
11–20	106	0	0
21–30	839	14	1.7
31–40	1866	53	2.8
41–50	2017	94	4.7
51–60	1768	145	8.2
61–70	713	75	10.5
71–80	138	15	10.9
81–90	11	4	36.4
Totals	7487	401	5.4

Proportion of patients with polyps by sex: 255 of 3,486 males, 6.8 per cent; 146 of 3,000 females, 3.9 per cent.
Statistics developed from data of Rider and Associates (10).

PREMALIGNANT CONDITIONS

The registry abstracts and maintains a follow-up on patients with the following neoplasms considered as either potentially premalignant or benign, and of special interest to various members of the staff: leukoplakia of the cheeks, esophagus, larynx, vulva, and bladder, malignant lentigo, senile keratosis, cornu cutaneum, teratoma of mediastinum, intraductal papillomas, proliferative cystic disease, florid adenosis of breast, gastrointestinal polyps and leiomyomas, benign islet cell and benign carcinoid tumors, cystadenoma of the ovary, benign nervous system tumors (neurofibromatosis), pituitary adenomas, thymomas, giant cell tumor of bone, aneurysmal bone cyst, eosinophilic granuloma, fibrous dysplasia, myeloid metaplasia, polycythemia rubra, secondary polycythemia, myxofibroma, glomus tumors, carotid body tumors, hemangiomatosis, papillomas of the bladder, parotid gland adenolymphomas and cylindromas, suspected cancers at any site. This is, in a sense, a prospective study designed to ascertain the incidence of malignancy in the organs harboring such nonmalignant lesions. Three examples follow:

Polyps of the colon and rectum. Among 7,487 patients subjected to proctoscopic examination, Rider and associates found that 401 had polyps of the rectum or colon, an overall incidence of 5.4 per cent. Table V shows the marked increase in incidence in patients over 50 years old. Subsequent follow-up and examination have revealed that about 40 per cent of these patients experienced recurrent polyps. During the 4 year follow-up after the group was closed, 16 (23 per cent) of the 70 deaths in the 401 patients were due to carcinoma of the colon.

Leukoplakia vulvae. Leukoplakia of the vulva without demonstrable carcinoma was diagnosed in 19 patients followed up between 1939 and 1958. Over this period, in 3 (17 per cent) of these patients carcinoma of the vulva has developed.

Intraductal papilloma of the breast. Eighty-one patients subjected to biopsy of a breast between 1944 and 1959 were found to have

intraductal papillomas without associated frank carcinoma. Of these, 6 were subjected to operation between 5 and 24 months later and found to have carcinoma. Five patients were found to have intraductal papillomas at the time of mastectomy for carcinoma of the breast, while 2 additional patients previously treated for carcinoma underwent removal of papillomas from the remaining breast 7 months and 2⅓ years later.

CONCLUSION

We have attempted to present a few of the areas in which a cancer registry adds to our knowledge of the disease and helps to measure the efficacy of our therapeutic procedures. The registry has rightfully focused attention on means of improving the data entered in the record as well as of presenting an evaluation of data that are available to the registry. A successful registry operation requires the co-operation of the staff and a large amount of clerical work. It is expensive. It does provide, however, definitive, factual information and answers to questions which so often are controversial because of conflicting opinions based on impressions and inadequate evidence.

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TREATMENT OF ADVANCED CANCER WITH 5-FLUOROURACIL

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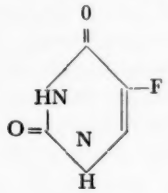
THE FLUORINATED PYRIMIDINE, 5-fluorouracil, was synthesized by Heidelberger and associates (3). The structural formula is:



They postulated that a compound of this configuration might be an effective chemotherapeutic agent in cancer, since uracil is utilized preferentially in the biosynthesis of nucleic acids in tumors, and nucleic acid analogues have been demonstrated to affect certain neoplasms in humans. Moreover, the substitution of fluorine for hydrogen in many classes of compounds has a pronounced biologic effect. 5-Fluorouracil was synthesized and subsequently screened as an antitumor agent in animals. It produced a significant effect on the growth of a wide range of transplantable tumors in mice, rats, and hamsters. Clinical trials demonstrated the effectiveness of the compound in certain human tumors. We have observed the effect of the drug in 50 patients with advanced cancer.

MECHANISM OF ACTION

5-Fluorouracil is an antimetabolite. It affects nucleic acid metabolism and thereby interferes with cell division. It is believed that 5-fluorouracil or one of its metabolites prevents the synthesis of deoxyribonucleic acid by blocking the methylation of deoxyuridylic acid to thymidylic acid. It also influences, but to a lesser extent, the synthesis of ribonucleic acid. These substances are essential for cell division, hence the effect on the proliferation of neoplasms and other tissues.

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ADMINISTRATION AND DOSAGE

The drug was administered intravenously according to the method of Curreri and associates. It did not produce pain or visible reaction, but repeated injections occasionally produced local vein thrombosis. The compound is supplied in ampules as a colorless liquid.

The basic course of 5-fluorouracil now recommended by Curreri and associates is 15 milligrams per kilogram per day, administered for 5 consecutive days. A daily dose of 1 gram is not exceeded, regardless of the patient's weight. This dosage schedule was reached by trial and error by Curreri and associates who gradually increased the dose until toxic manifestations occurred. Larger doses were found to be excessively toxic and smaller doses were ineffective. The dose for obese patients is calculated on the basis of ideal weight rather than actual weight. Studies with the carbon-labelled compound have shown little or no uptake of the drug by fat, according to Heidelberger and associates (4). Patients who have previously received cancer chemotherapy or extensive roentgen therapy may not tolerate a full course of 5-fluorouracil, and extreme caution is indicated under these circumstances. If the patient's general condition permits, a cautious attempt may be made to increase the course beyond the basic 5 dose

FIG. 1. Stomatitis with pseudomembrane on the lower lip.

schedule. An additional one-half dose may be administered on the seventh, ninth, eleventh and thirteenth days, unless signs of toxicity appear, such as stomatitis, severe diarrhea, or leucopenia, but a total of 7 doses is not exceeded during any one course as specified by Ansfield and Curreri. The injections are repeated at intervals of 4 to 6 weeks, depending upon the degree of toxicity and response of the tumor.

We are currently evaluating the toxic and therapeutic effects of prolonged intravenous administration.

TOXICITY

5-Fluorouracil is a potentially toxic drug at the dose level described. With perhaps rare exceptions it is necessary to produce clinical toxicity if regression of the tumor is to be anticipated. It is desirable that therapy be supervised by a physician who is particularly interested in cancer chemotherapy. Casual or indiscriminate use of the drug may do more harm than good. With careful control, severe toxic manifestations will rarely occur.

The most important toxic effect of 5-fluorouracil is depression of the bone marrow. In most of the patients herein reported, leucocyte counts were performed every other day, beginning the day treatment was initiated, and continued until normal levels were restored. The maximum depression of leucocytes occurred on or between the sixteenth and twenty-first days after the first injection in 70 per cent of patients. The nadir occurred between the thirteenth and fifteenth days in 12 per cent, and between the twenty-second and twenty-fifth days in the remaining 12 per cent. Three patients expired within a few days of initiation of therapy and are not considered. Using these data as a guide, we now study the peripheral blood less frequently. A blood count is obtained prior to therapy, and, if normal, is repeated every other day during the third week after the initial injection. With minimum laboratory effort and expense the lowest count usually will be included. Daily counts were made when severe depression was encountered and were continued until normal levels were re-established.

All leucocyte counts were within a normal range prior to 5-fluorouracil therapy. Significant depression, $<3{,}000$ leucocytes per cubic millimeter, occurred in 64 per cent of the patients. In 11 per cent of the patients the count was below 1,000 per cubic millimeter, and in 23 per cent the count was between 1,000 to 2,000 per cubic millimeter. The polymorphonuclear leucocyte was most severely affected. It represented less than 25 per cent of the circulating leucocytes at the point of greatest depression in 60 per cent of the patients. The number of polymorphonuclear leucocytes dropped to less than 10 per cent in one-third of all patients. Antibiotic coverage was instituted when marked depression occurred and was maintained until the count returned to near normal or normal levels. This usually required 7 to 10 days. Normal levels were re-established with amazing rapidity, considering the severity of the depression. Subsequent courses do not as a rule produce a more severe depression, but such may occur. There were 2 deaths attributable to sepsis, from slough of oral mucosa and bronchopneumonia, and from septicemia and bronchopneumonia. Several other patients were noted to have bronchopneumonia at autopsy. Since the latter is a common finding

in patients dying of cancer, it is illogical to assume that the drug was always responsible for its presence.

Platelet counts were performed in most patients and an occasional depression was noted, paralleling in general the time curve of leucocyte depression. Petechiae developed in 2 patients but did not correlate temporally with platelet depression. Frank hemorrhage occurred in 1 patient with a gastric cancer and in 1 patient with a carcinoma of the colon, but this complication did not seem to be chronologically related to therapy in the former patient.

Disturbance of gastrointestinal function during or immediately after therapy occurred in the majority of patients but was not a serious problem. Anorexia occurred in approximately 40 per cent of the patients, nausea in 25 per cent, and vomiting in 20 per cent. Ordinarily these symptoms were mild and did not compare in severity with the gastric upset noted in patients given nitrogen mustard. Diarrhea occurred in 17 of the 50 patients, 34 per cent, but was severe in only 3. Severe diarrhea is an indication for cessation of therapy.

In two-thirds of the patients stomatitis developed, which, in most instances, was of little consequence other than producing mild discomfort (Fig. 1). In several patients a pseudomembrane formed over much of the mucosal surface of the lower lip, and in a few others the oral mucosa was involved more extensively. In 1 patient, previously noted, a severe slough of almost the entire oral mucosa occurred.

A peculiar type of mental confusion occurred in 4 patients. These individuals were somewhat disoriented but responded to command and answered certain questions intelligently. It occurred within a few days of the initial injection and persisted for only a few days. Complete recovery followed. This complication was noted during each of several courses in 1 patient, but occurred only once in another patient who received 8 courses of the drug. The latter patient expressed the sensation as "I feel funny and I know I'm acting funny, but there isn't anything I can do about it."

FIG. 2. Nail changes associated with 5-fluorouracil therapy.

An eczematous rash, particularly over the bridge of the nose and cheeks, developed in a few patients. Pruritus occurred in several patients. Alternate pigmented and nonpigmented bands, representing each course of 5-fluorouracil therapy, developed in the nail beds of a number of patients (Fig. 2). Loss of hair, varying in severity, occurred in 13 patients or 26 per cent. Hair loss was mild and of little cosmetic significance in 7, but a definite thinning or near baldness occurred in the other 6. One of these was a female who was made almost completely bald. Noticeable regrowth occurred with the omission of a single course of therapy. One patient was readmitted to the hospital in diabetic coma after a second course of 5-fluorouracil. The relationship of the therapy is debatable, but the diabetes had not been recognized previously.

CLINICAL MATERIAL

Patients were selected for 5-fluorouracil therapy only when conventional treatment was not applicable. Sixteen patients had received prior chemotherapy or irradiation or both. In these 16 patients there were no severe toxic manifestations, and no deaths were attributed to the use of the drug.

Thirty-one of the 50 patients in our series

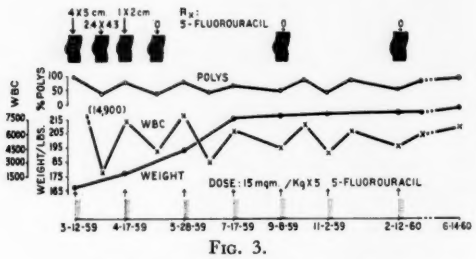

FIG. 3.

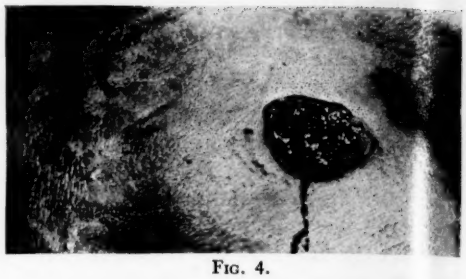

FIG. 4.

FIG. 3. Clinical course of one patient.
FIG. 4. Pretreatment appearance of the lateral gluteal mass in the patient referred to in Figure 3.

fall into the poor risk category defined by Ansfield and Curreri. They include patients in a poor state of nutrition, those with marked protein loss from effusion, those with a history of extensive pelvic irradiation or prior therapy with alkylating agents, those with widespread bone metastases or liver dysfunction with jaundice, and those subjected to major surgical procedures within 30 days prior to therapy.

Almost all patients received 5 doses of 15 milligrams per kilogram during each course of therapy. A few patients received slightly more, a few received slightly less. The courses were repeated at intervals of approximately 5 to 6 weeks.

Gastrointestinal tract. Seventeen patients with primary malignant tumors of the gastrointestinal tract were treated. All had been subjected to surgery, either resectional or exploratory, and were suffering from persistent disease. Nine tumors were primary in the colon or rectum. Six of the 9 showed transient benefit after 5-fluorouracil therapy. Responses included marked relief of discomfort at the site of a nonresectable rectal neoplasm, decrease in the size of a recurrent abdominal mass, failure of reaccumulation of pleural effusion in a patient previously requiring repeated thoracenteses, and lack of progression of enlarging pulmonary metastases. When one evaluates these 9 patients on a critical basis, taking into consideration the degree of objective or subjective response, activity of the patient, and length of survival after treatment, only 2 can be considered to have received worthwhile benefit. Six patients with gastric cancer were treated without objective benefit in any, although 4 of the 6 noted transient subjective improvement. In no instance was significant or sustained improvement manifest. One patient with recurrence of a carcinoma of the anal canal and 1 with a nonresectable esophageal cancer were treated, without benefit. Four of these 17 patients are alive, but their general condition has progressively deteriorated, and none is expected to survive much longer. All patients have survived less than 1 year since the initiation of 5-fluorouracil therapy.

Breast. Three patients with cancer of the breast were treated; a definite objective response occurred in all. One patient with a rapidly progressing chest wall recurrence, cutaneous nodules, and an extensive inflammatory blush showed definite regression with each course of 5-fluorouracil, but further growth occurred during the intervals between courses. A patient with extensive liver metastases had undergone radical mastectomy 6 years prior to admission. There was a slight decrease in size of the liver, 20 pounds gain in weight, and immeasurable symptomatic improvement. She is able to perform all the duties of a housewife and is clinically well 9 months after her initial injection. In the third patient, several cutaneous nodules disappeared but she expired 1 month later from complications of therapy.

Urinary bladder. Three patients with ad-

vanced cancer of the urinary bladder were treated. Two of these had no significant response. The third patient had a large metastatic epigastric mass which completely disappeared clinically, and there was marked diminution in the size of an iliac mass. The progressively downhill course of his disease was temporarily interrupted, but he expired about 6 months after the initial course of the drug. He is considered to have been minimally benefited by the drug in terms of worthwhile survival.

Melanoma. Three patients with disseminated melanoma were treated without effect. All died in less than 2 months.

Lung. 5-Fluorouracil was administered to 5 patients with advanced lung cancer. The primary tumor had been unresectable or inoperable in all, and in 3 there was extensive dissemination at the time of treatment. One patient was treated after the lesion was found to be nonresectable at exploratory thoracotomy. The tumor was relatively small, and there was no evidence of disseminated disease, but progression of the disease was not affected. In none was there subjective or objective improvement.

Head and neck. Twelve patients with advanced cancer of oral, laryngeal, or pharyngeal origin were treated. All but 3 had previously received surgical or roentgen therapy. In these 3 patients the disease was so far advanced on admission that even palliative radiation was not considered feasible. Eleven patients had metastases in the cervical lymph nodes.

One patient had received roentgen therapy for a lymphoepithelioma of the nasopharynx. On admission he was considered terminal. There were fixed cervical lymph node metastases and pulmonary metastases. He was in considerable pain. With each course of 5-fluorouracil there was relief of pain, regression of lymph node metastases, and general improvement. Lung metastases failed to show regression but did not increase in size. He expired approximately 11 months after starting treatment but was markedly benefited for a period of several months.

FIG. 5. Posttreatment appearance showing complete healing of the ulcer and disappearance of the mass in the same patient as shown in Figure 4.

Six patients had laryngeal or hypopharyngeal neoplasms. Minimal, though definite, objective or subjective improvement was noted in 5, but was short-lived in all. Benefit to any was questionable.

Five patients with cancer of the oral mucosa were treated, and 4 of these experienced objective and subjective benefit. In 3 the regression of the primary lesion was so marked that they are considered benefited although the posttreatment period has been brief. Regression of the oral lesion was noted within a few days of treatment and continued for 2 to 3 weeks. Regrowth then occurred and progressed rather rapidly until the drug was again given. Decrease in size of lymph node metastases also occurred. Complete disappearance of either the primary tumor or metastases was unusual.

The ability to visualize the primary tumor, we believe, accounts for the high incidence of objective improvement in patients with oral, laryngeal, and pharyngeal cancer. A comparable decrease in size of a gastric neoplasm would usually not result in classification as objective improvement because the tumor is not directly visible and regression is not apparent. Accessibility may also be a factor in the frequent objective improvement noted with breast cancer.

Miscellaneous tumors. Three patients with pancreatic cancer were not improved, nor was 1 patient each with widely disseminated seminoma, osteogenic sarcoma, and soft tissue sarcoma.

One patient with a tumor of undetermined histologic nature and origin has had a dramatic and prolonged response (Fig. 3). This patient, a 39 year old male, had an abdominal mass in the right lower quadrant extending into the inguinal region. The cecum was displaced medially, and the right ureter was obstructed. Exploratory surgery elsewhere provided tissue variously interpreted as undifferentiated carcinoma, melanoma, and reticulum cell sarcoma by several pathologists. Lack of regression of the mass after vigorous roentgen therapy would seem to eliminate the last mentioned histologic possibility. Prior to initiation of 5-fluorouracil therapy an ulcer developed over the upper gluteal region (Fig. 4). He had continuous severe pain in the right hip and was bedridden. Survival for longer than a few weeks was not anticipated. Dramatic improvement occurred within a few days of the initial course of therapy. The abdominal mass disappeared, the ulcer healed (Fig. 5), the ureter was no longer obstructed, and he is free of pain and has gained 60 pounds. He returned to work within 2 months and is working full time 15 months later.

DISCUSSION

5-Fluorouracil is capable of producing a definite though limited effect in some patients with malignant neoplasms of epithelial origin. In our experience with 50 patients receiving 130 courses, approximately one-third of all patients manifested objective regression and approximately one-half were subjectively benefited, at least to a minimal degree. In the majority of these patients the effect was limited and improvement was transient. An arbitrary clinical evaluation based on the nature and duration of survival indicates that 10 patients received what we consider worthwhile palliation. In 5 of these it has been minimal and relatively transient. In only 1 individual have the results been truly dramatic.

The 12 surviving patients are, with 3 exceptions, going progressively downhill, and long survival is not anticipated. The fact that 15 patients survived less than 1 month, 28 less than 2 months, and 31 less than 3 months, emphasizes the advanced nature of the disease in these individuals. It also suggests that if meager benefit can be obtained in patients in this stage of disease, better results might be obtained in patients whose disease is less advanced. This, we fear, is false optimism, as our best results occurred in patients who were nearly moribund, and many with rather limited though irremovable disease ran a rapid downhill course.

The toxicity of the compound, and the rapid regrowth of tumors which initially regress are the two main disadvantages of 5-fluorouracil therapy. The latter requires the administration of repeated courses of the drug; the former necessitates frequent laboratory and clinical evaluation. Together, they require almost continuous supervision by the attending physician with considerable expenditure of time and money. There is no doubt that the drug has merit, but unfortunately its liabilities often outweigh its assets. It has a place in the management of advanced cancer, but it is relatively narrow and as yet not well defined.

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CLINICAL OBSERVATIONS OF CONDITIONS WHICH APPARENTLY ENHANCE MALIGNANT CELL SURVIVAL

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CONTROVERSY EXISTS as to whether malignant cells which eventually grow and form metastases in certain organs rather than in others do so because of mechanical factors controlling the distribution of exfoliated cells or because of local factors resulting in different rates of growth in the different organs. Briefly, the mechanical thesis is that the tumor cells are distributed according to the vagaries of the circulatory system. This thesis gained supporters when the vertebral venous system was described by Batson. Further, the work of physiologists showing that large particles ranging in size from 50 to 300 microns would pass through the capillary beds of various organs by way of arteriovenous and venous-venous shunts gave support to the idea that the capillary networks in the lungs and in other organs were less of a barrier than they had been thought to be.

On the other hand, it has been conclusively demonstrated by Engell and by Moore and associates (7) that most tumors release numerous cancer cells more or less continuously into the lymphatic or vascular systems or both. This exfoliation of cells varies according to the kind of tumor, its size, and the site of origin. Thus, one would have to conclude that the vast majority of these cells are destroyed either in the blood stream or after lodging in various organs, since relatively few patients die with more than a limited number of metastases. The thesis that tumor cell survival is determined by local factors at the site of lodgment has always been intriguing, but there has never been good clinical or experimental evidence to support this view.

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In the experimental laboratory, millions of tumor cells may be injected into a systemic vein and yet the metastases which subsequently grow are often limited to one or several sites; such metastases are most abundant in the lung and usually much fewer in the kidneys and the liver. On the other hand, skeletal muscle and the brain are almost never sites of metastases. In this laboratory, thousands of mice have received intravenous injections of as many as 3,000,000 to 10,000,000 cells without a brain metastasis developing in a single mouse. Paradoxically, the brain is an excellent site for assaying the growth of even one cell when the cell is injected directly into it. Experiments in which brain or muscle has been macerated and then injected into recipient mice have shown that tumor cells are present in these organs but are somehow unable to develop into metastases under normal conditions.

The pretreatment of mice with cortisone results in a preferential growth of metastases in the liver rather than in the lungs. This puzzling phenomenon has not been explained. Iversen and Hjort reported that of 31 patients dying with disseminated breast cancer who had been treated with cortisone, prednisone, or both, 8 had spleen metastases, whereas a similar group of patients not treated with corticoids had none.

Metastases or implants or both have been reported to be more frequent in animals conditioned by roentgen rays, cortisone, chemotherapeutic agents, formalin, hypochlorite, and other chemicals and at sites of injured tissue. Some of these observations have parallels in clinical medicine. Cancer implants have been reported to occur in surgical wounds, bowel anastomoses, trocar punc-

FIG. 1.

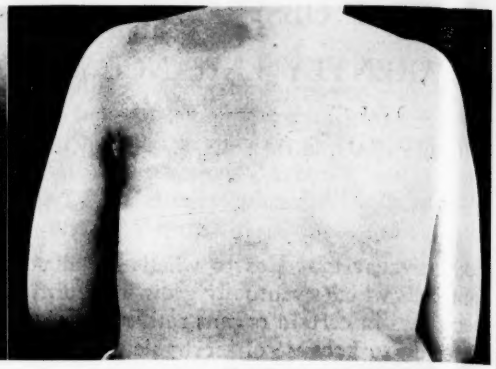

FIG. 2.

FIG. 1. Extensive dermal metastases in the patient in Case 1 one year after mastectomy and radiation. Note the cutaneous metastases confined within the ports of radiation.
FIG. 2. Cutaneous metastases in the irradiated area in the same patient.

tures, sites of benign ulcers, and in areas of lymphatic stasis, according to Haverback and Smith.

METASTASES AFTER ROENTGEN IRRADIATION

At the Roswell Park Memorial Institute, we have observed a series of patients who have had roentgen ray therapy for carcinoma of the breast and in whom have subsequently developed hundreds of metastases limited to the areas of the superficial skin that had been exposed to roentgen radiation.

CASE 1. A 46 year old woman first noted a mass in the left breast in April 1958 and underwent radical mastectomy 5 months later. Pathologic examination revealed that 6 of 11 axillary nodes contained metastatic carcinoma. In November 1958, 2 months after surgery, she received radiation in the left anterior chest and supraclavicular axillary regions. A total skin dose of 3,400 roentgens was given to all 3 ports. In November 1959, the patient noticed recurrent skin metastases over the portion of the left chest wall which had been exposed to radiation and a lump in the contralateral breast. Roentgen ray therapy was again directed to the left anterior chest wall and also the right breast. A total skin dose of 2,600 roentgens was delivered to the left anterior and anterorlateral portion of the chest wall, and a total of 3,000 roentgens anteriorly to the right breast. The factors used were 200 kilovolts, half value layer of 1.0 millimeter of copper, and skin target distance of 50 centimeters. The patient was then referred to the breast service of the institute in March 1960 for consideration of further therapy.

Examination revealed massive dermal metastases over the left anterior part of the chest wall, the shoulder, and subscapular area. The skin metastases were almost entirely confined within the area of roentgen ray ports and along the margins of the radiation dermatitis (Figs. 1 and 2). Examination of other systems was essentially negative. The patient had a bilateral oophorectomy on 16 March 1960. No remission of disease has been observed.

CASE 2. A 70 year old woman first noticed a mass in the right breast in March 1955. Three months later, she was referred to the breast service for diagnosis and treatment. Examination in June 1955 revealed a 3.0 by 4.0 centimeter mass in the upper inner quadrant with dimpling of the skin. A large, clinically malignant axillary mass measuring 10 by 7 centimeters and accompanied by several small nodes was also noted. Biopsy of the breast and the axillary mass revealed carcinoma. The lesion was considered inoperable and was treated by radiation in June 1955. A total tumor dose of 4,698 roentgens was given to the right axilla and supraclavicular regions and 3,162 roentgens to the breast. A simple mastectomy was performed in October 1955 because of an impending ulceration of the growing tumor. In February 1959, supraclavicular metastases became evident and were again treated with radiation. A total of 3,887 roentgens was given to the right supraclavicular region. The factors used were 200 kilovolts, half value layer of 0.9 millimeter of copper, and skin target distance of 50 centimeters. By September 1959, numerous dermal metastases were evident confined almost completely within the ports of radiation (Fig. 3). The boundary of the metastases coincided with that of the radiation dermatitis. The patient had a bilateral adrenalectomy in December 1959. No regression of metastases has been observed.

CASE 3. A 64 year old woman was referred to the

breast clinic in November 1959 because of a mass in the right axilla near the tail of the breast. Biopsy of this mass revealed carcinoma. Her history dated back to June 1957, when she had had a cervical biopsy and a tentative diagnosis of adenocarcinoma of the fundus had been made. At the time of biopsy, a total of 25 milligrams of radium was placed in the uterine cavity and was kept there for 152 hours, or 3,800 milligram hours. In July 1957, a total abdominal hysterectomy and salpingo-oophorectomy was performed. After the operation, 20 roentgen ray treatments were given, dose unknown. The patient did well until February 1959, when swelling of the left leg was noticed. As the swelling increased and involved both legs, another course of radiation was given to the abdomen, but with no effect. In early January 1960, a few skin metastases were observed over the lower abdominal wall. Biopsy of the dermal lesion revealed carcinoma. Dosage with cortisone, 50 milligrams daily, was started. A week later, when the patient was seen again in the clinic, a fantastic progression of disease was shown by extensive dermal infiltration with cancer over the lower abdominal wall. The skin metastases were confined within the ports of radiation (Fig. 4). Tumor infiltration of skin was also observed along the incision of the breast biopsy. The patient refused hospitalization and has since been managed by her family physician.

FIG. 3. Massive dermal metastases occurring in the irradiated area 4 years after mastectomy and radiation.

METASTASES AFTER LYMPH NODE DISSECTION

Another clinical observation attesting to the importance of local environmental factors is the appearance of multiple superficial metastases in the legs of patients who have had a groin dissection. For example, it is not uncommon, in a patient who has had a primary malignant melanoma of the foot removed and has subsequently had a groin dissection, for many superficial metastases to develop in the skin of the afflicted leg after months or even years. The contralateral leg is usually free of disease. Studies in this and other institutions have indicated that malignant melanomas are often accompanied by a continued release of tumor cells into the peripheral and vascular systems. It would seem strange, therefore, that all of the superficial skin metastases in these cases are located in the leg below the level of the groin dissection, unless the local environment has been altered so as to favor tumor cell growth. One might conclude that the groin dissection, by disrupting the major lymphatic vessels that drain the limb, has caused these tumor cells to be arrested in the lymphatics or capillaries and has thus produced a favorable environment for their survival. Vascular stasis may be present but usually to a lesser degree.

CASE 4. A 51 year old white male had noticed a small lesion on the dorsum of the middle toe of the left foot in 1953. This was originally treated as a corn, but a subsequent diagnosis of amelanotic melanoma led to amputation. In January 1955, a groin dissection was performed at another hospital. A year after the radical groin dissection, the patient noticed a small lump in the skin of the left thigh. Biopsy revealed melanoma. A few months later, more skin nodules appeared distal to the groin dissection. He was then referred to this institute in 1956 for further therapy.

The previous pathologic slides were reviewed at this institute and a diagnosis of lymphangioendothelioma was made. A hemipelvectomy was recommended, but the patient refused the operation. In June 1957, more skin nodules appeared in the left thigh. These nodules were excised by a surgeon and the area was grafted. By September 1957, the skin lesions had become more extensive, covering the grafted area and the entire anteromedial and lateral aspects of the thigh just below the groin dissection scar (Fig. 5).

In December 1957, pleural effusion developed and the pleural fluid was shown to contain cancer cells. He was again referred to this institute and was treated with actinomycin D. The condition remained unchanged during the treatment with actinomycin D. From January 1958 to January 1959, the pleural effu-

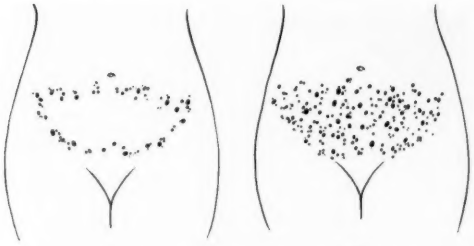

FIG. 4. Appearance of recurrent cutaneous metastases in a woman with cancer of the uterus 3 years after abdominal hysterectomy and pelvic irradiation. a, Note the distribution of tumors within the ports of irradiation over the abdominal wall. b, Rapid increase of skin lesions a week after cortisone therapy.

sion became worse, requiring numerous thoracenteses. Triethylenethiophosphoramide was injected into the thoracic cavity after each thoracentesis. Since then, various chemotherapeutic agents, including methylgloxalbisguanylhydrazone and cytoxan (cyclophosphamide), have been given to the patient with no evidence of improvement. At the present time, he is in the hospital dying of the disease.

DISCUSSION

These clinical observations are relevant to the general problem as to whether survival and growth of metastases depend more on mechanical and circulatory factors or on a favorable local environment. Our clinical observations support the latter possibility. Obviously, the cells must reach the sites of metastases before growth can occur, but the predominant factors determining whether or not cells will survive and grow are the local environment and, to a lesser extent, the systemic milieu.

Further, these observations are of interest in shedding light on the question of the dormancy of malignant cells. It has been stated that the "moment of truth" for tumor cells is the time when they first lodge in a capillary bed—that they must either survive or perish. This statement is somewhat erroneous, as is indicated by many clinical observations showing that tumor cells may remain dormant for months or years and subsequently multiply and kill the host. The exact nature of the dormancy of tumor cells is not known. It is not clear whether tumor cells lie dormant intracellularly in phagocyte-like cells or extracellularly in one or another of the constituents of connective tissues. For example, the role of the fibrin which seems to envelop most tumor cells is not clear.

FIG. 5. Extensive recurrent tumors along the anterior and lateral aspects of left thigh and leg distal to the groin dissection in a patient with hemangioendothelioma.

The factors which allow dormancy to be terminated and cell growth to be reinitiated are also unknown. Clinical observations suggest that these factors are systemic, since the regrowth of metastases after a period of many years may often occur simultaneously in all parts of the body. Very little experimental work has been done in connection with this clinical phenomenon. The excellent work of the Fishers demonstrated that operative manipulation would activate dormant cells in the liver of animals injected with Walker 256 sarcoma. Like others, we have noted the effectiveness with which cortisone may reduce the animals' defenses and allow survival of very small numbers of cells (6). Similarly, Pelner has observed the apparent flare-up of malignant lesions in some patients who were treated with corticoids for one or another of the diseases of the connective tissues.

We have purposely avoided discussion of the possible role of orthodox immunologic phenomena in this paper because of the lack of strong evidence of specific tumor antibody formation despite numerous investigations and because of our desire to focus attention on the importance of local factors. In any event, it would seem important to catalogue further examples of clinical phenomena related to such changes in the local environment of tumor cells as may result in accelerated tumor growth.

SUMMARY

1. Patients with breast cancer have been noted to have multiple recurrences in areas

previously treated by roentgen-ray therapy.

2. In patients with various kinds of malignant lesions of the terminal part of a limb superficial multiple metastases distal to possible lymph node dissections have been shown to develop. The relationship of these two procedures to the creation of lymphatic or vascular stases which might provide a favorable environment for the growth of tumor cells is briefly discussed.

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EFFECTS OF ENDOCRINE HOMOGRAFTS ON THYROID AND PARATHYROID FUNCTION

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THERE HAVE BEEN numerous reports of patients with endocrine deficiencies who have been treated by homografts of endocrine tissues. The technique of homografting has varied greatly, and fetuses of different ages, newborn infants, and adults have been used as donors. There has not been a patient reported in whom histologic survival of a homograft has been demonstrated after the well defined period in which homograft rejection occurs. Despite the failure of histologic survival, varied techniques, and donor tissues, there have been numerous reports of clinical improvement of endocrine-deficient patients after homotransplantation of endocrine tissues. This is a report of 5 patients who were hypothyroid or hypoparathyroid or both and who have received homografts of adult endocrine tissues.

In this study, homografts of parathyroid or thyroid tissues or both were obtained from adult patients who were undergoing subtotal thyroidectomy. The tissues were sliced approximately 2 to 3 millimeters thick and approximately 2 to 5 grams were placed between the rectus abdominis muscle fibers, beneath the rectus fascia, and in the deep subcutaneous tissues of the abdominal wall. Local anesthesia was used for the adult recipient patients and general anesthesia was used for the infant. Several sections of tissue for implantation were examined histologically.

There were no systemic signs of an allergic reaction after transplantation of foreign tissue in any patient. Medications such as antihistaminics were not given. There were signs of a localized allergic reaction at the site of transplantation in the infant whose abdominal wall was thin and in 1 adult in whom the transplant was placed in the subcutaneous tissues only. A visible area of redness, increased heat, and swelling developed within 12 to 18 hours in these 2 patients. These findings subsided gradually over a period of several days. All adult patients complained of moderate pain at the site of transplantation during the first postoperative week.

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CASE REPORTS

CASE 1. A male infant was born at the Georgia Baptist Hospital on 22 August 1959. The mother was Rh negative, gravida 5, para 4; she was noted to have polyhydramnios during pregnancy but there was a normal, spontaneous delivery. The infant was blood type A, Rh negative; the birth weight was 7 pounds, 12 ounces. At approximately 24 hours of age the infant had a transient period of cyanosis associated with considerable mucus. Otherwise, the newborn hospital stay was not remarkable. The infant was readmitted at 5 weeks of age because of convulsions and diarrhea. Subdural taps were performed and found to be dry, and findings from lumbar puncture were normal. Sulkowitch urinary assays were 2 plus. The convulsive seizures responded fairly well to phenobarbital, and the patient was discharged on a regimen of ⅛ grain phenobarbital every 8 hours.

The patient was readmitted at 8 weeks of age with intermittent convulsions. The serum calcium was 5.1 milligrams and the phosphorus was 7.8 milligrams per 100 milliliters. Convulsions were controlled with dilantin, phenobarbital, and intermittent intravenous injections of calcium gluconate. The infant was treated with calcium chloride, maalox, vitamin D, and A.T. 10 preparations from 24 October 1959 to 8 December 1959. Despite this regimen, he continued to have twitching and convulsive movements. The serum calcium varied between 5.2 and 7.1 milligrams and the phosphorus between 6.5 and 8.8 milligrams per 100 milliliters. The serum protein bound iodine was 5.0 micrograms per 100 milliliters. Roentgenograms taken 17 November 1959 showed demineraliza-

tion and cupping at the distal ends of the long bones. A modified Ellsworth-Howard test performed on 25 November 1959 showed a twofold increase in urinary phosphorus excretion. On 8 December 1959 thyroid and parathyroid tissue removed from an adult female patient having a subtotal thyroidectomy for nontoxic nodular goiter was homografted into the abdominal wall of the infant. On the tenth postoperative day the 24 hour urinary phosphorus excretion was 3 times greater than it had been preoperatively. The serum calcium-phosphorus ratio was reversed toward normal for the first time on the eleventh postoperative day, the serum calcium being 7.2 milligrams and the phosphorus 6.2 milligrams per 100 milliliters. Roentgenograms taken on the eighteenth postoperative day showed beginning recalcification at the ends of the long bones. The serum calcium concentration increased progressively after the eleventh postoperative day. On the twenty-fourth postoperative day the serum calcium was 9.3 milligrams and the phosphorus was 5.9 milligrams per 100 milliliters. Medications were decreased progressively until they were discontinued on the forty-first postoperative day. On 7 June 1960 the serum calcium was 9.2 milligrams and the phosphorus was 4.8 milligrams per 100 milliliters. There have not been any convulsions since homotransplantation of the thyroid-parathyroid tissue.

It is believed that this patient had idiopathic hypoparathyroidism or hypocalcemic tetany of the newborn. It was extremely difficult to control the hypoparathyroidism by a medical regimen. Roentgenograms of the long bones taken at 3 months of age were consistent with rickets, and this condition is believed to have been caused by lack of available calcium for mineralization. Improvement after homotransplantation was progressive and dramatic; 7 months after homografting, the patient is doing well without medication.

CASE 2. A 57 year old female was first seen at Piedmont Hospital in January 1958. In June 1955 she had had a subtotal thyroidectomy for treatment of a toxic goiter. Postoperatively signs and symptoms of hypothyroidism and hypoparathyroidism developed coincident with a reduction of blood calcium concentration and an elevation of blood phosphorus level. From that time until April 1958 she was maintained with difficulty on a regimen including calcium lactate, vitamin D, amphojel, and desiccated thyroid. The patient continued to have intermittent episodes of tetany requiring intravenous administration of calcium gluconate. On 30 April 1958 a homograft of thyroid-parathyroid tissue taken from a 5 month old fetus was placed into her neck. The patient had no episodes of tetany for 1 month after the transplant, during which time she was maintained on the same medical regimen she had been on preoperatively. On 27 May 1958 she began to have tetany again and there was difficulty in controlling the disease medically. On 20 July 1958 a second homograft of thyroid-parathyroid tissue taken from a 5 month old fetus was placed into her neck. There was a chemical and clinical response within 1 week of this operation. At the time of discharge from the hospital 3 weeks later the serum calcium concentration varied between 12 and 17 milligrams per 100 milliliters. The patient did not have signs or symptoms of hypoparathyroidism or hypothyroidism during the following year. Her only medication was 50,000 units of vitamin D each day. Repeated calcium and phosphorus determinations were within normal limits. Fourteen months after the effective homograft the patient again began to have intermittent episodes of tetany. She was placed on a medical regimen but her serum calcium could not be elevated above 7.5 milligrams per 100 milliliters. On 23 September 1959 thyroid-parathyroid tissue taken from an adult female having a subtotal thyroidectomy for nontoxic nodular goiter was homografted into the abdominal wall of the patient. On the fifth postoperative day the serum calcium was 10.7 milligrams, and the phosphorus was 4.5 milligrams per 100 milliliters. Medications were decreased progressively until they were discontinued on the fourteenth postoperative day. The patient was asymptomatic until the thirty-fifth postoperative day when symptoms of hypothyroidism and hypoparathyroidism recurred. At that time the serum calcium level was 8.4 milligrams, and the phosphorus was 4.2 milligrams per 100 milliliters. Between that time, 28 October 1959 and 3 December 1959, the serum calcium varied between 6.2 and 8.9 milligrams per 100 milliliters, and she had intermittent tetany despite a medical regimen of calcium lactate, vitamin D, amphojel, and desiccated thyroid. Although the serum calcium was low during this time, the serum phosphorus was never greater than 5.0 milligrams per 100 milliliters. Of further interest is the fact that, coincident with recurrence of hypoparathyroidism, clinical symptoms of profound hypothyroidism developed and the serum protein bound iodine level varied between the low levels of 1.6 and 2.6 micrograms per 100 milliliters even though 3 repeated determinations of radioactive iodine uptake over the site of abdominal transplant was from 9 to 13 per cent; uptake over the neck was 3 to 5 per cent.

On 3 December 1959 thyroid tissue only that was taken from an adult female having a subtotal thyroidectomy for nontoxic nodular goiter was homografted into the abdominal wall of the patient. A block of tissue from the abdominal wall at the site of the previous transplant was excised at this time. Histologic examination of this tissue showed chronic inflammation and foreign body granulomas in fibrous tissue and muscle. No thyroid tissue was recognized.

On the seventh postoperative day the serum calcium was 9.8 milligrams, and the phosphorus was 4.3 milligrams per 100 milliliters. Medications were decreased progressively until they were discontinued on the twentieth postoperative day. The patient has not had tetany since this last homograft, and she was asymptomatic and not taking any medication 7 months after transplantation. The serum calcium has ranged from 9.0 to 12.2 milligrams per 100 milliliters. Repeated determinations of radioactive iodine uptake over this site of the second abdominal transplant have ranged from 9 to 13 per cent.

This patient with postoperative hypothyroidism and hypoparathyroidism has had a prolonged beneficial response to 1 of 2 fetal tissue homografts and to 1 of 2 adult tissue homografts. It should be emphasized that adult thyroid tissue only was homografted on 3 December 1959, and the signs and symptoms of hypoparathyroidism responded equally as well as did those of hypothyroidism.

CASE 3. A 59 year old female was first seen at Piedmont Hospital on 9 January 1960. In 1942 she had had a subtotal thyroidectomy for treatment of a toxic goiter. Postoperatively stridor and signs and symptoms of hypothyroidism and hypoparathyroidism developed. From that time until admission she was maintained with difficulty on a medical regimen including calcium gluconate orally and intravenously, vitamin D, parathormone, and desiccated thyroid. She had continual tingling of her extremities and intermittent episodes of tetany. She began to have increasing difficulty in breathing several months prior to admission, and a tracheotomy and laryngoscopy were performed on 16 January 1960. The right vocal cord was fixed and excessively thickened by scar. On admission the serum calcium was 4.8 milligrams, and the phosphorus was 7.1 milligrams per 100 milliliters. The patient was placed on a medical regimen of 8 grams of calcium lactate, 100,000 units of vitamin D, amphojel, and 2 grains of desiccated thyroid per day. After 9 days of this treatment, the serum calcium was 5.0 milligrams, and the phosphorus was 6.4 milligrams per 100 milliliters. At that time, 18 January 1960, thyroid and parathyroid tissue taken from an adult female having a subtotal thyroidectomy for nontoxic goiter was homografted into the abdominal wall of the patient. On the eighteenth postoperative day the serum calcium was 6.4 milligrams, and the phosphorus was 6.8 milligrams per 100 milliliters. On the thirty-ninth postoperative day the serum calcium was 10.0 milligrams, and the phosphorus was 6.3 milligrams per 100 milliliters. Serum protein bound iodine was 3.4 micrograms per 100 milliliters. Calcium lactate, vitamin D, and amphojel were discontinued. One month later, 21 April 1960, the serum calcium was 9.4 milligrams, and the phosphorus was 4.9 milligrams per 100 milliliters. Serum protein bound iodine was 4.4 micrograms per 100 milliliters.

Seven months after homografting, the patient had no symptoms of hypoparathyroidism. The serum calcium was 9.0 milligrams, and the phosphorus was 6.0 milligrams per 100 milliliters on 7 July 1960. However, the protein bound iodine was 2.3 micrograms per 100 milliliters on 26 May 1960, and the patient has been maintained on 2 grains of desiccated thyroid per day since that time. The serum protein bound iodine on 7 July 1960 was 6.0 micrograms per 100 milliliters. It is of interest that the patient has not had tingling or tetany since being placed on this medical regimen and having a homograft, even though the serum calcium was only 6.4 milligrams on the eighteenth postoperative day. Uptake of radioactive iodine over the site of abdominal transplant 3 months after homografting was 10 per cent; uptake over the neck was 4 per cent.

Dunphy and Jacob have pointed out that the majority of reported hypoparathyroid and hypothyroid patients having parathyroid and thyroid homotransplants have been free of signs and symptoms of hypoparathyroidism for periods ranging from a few weeks to 2 years but have had recurrence of signs and symptoms of hypothyroidism in much shorter periods of time. This patient had recurrence of signs and symptoms of hypothyroidism 4 months after homografting but she continues to be free from signs and symptoms of hypoparathyroidism and she does not require medication.

The time interval between operation and response of the serum calcium and phosphorus to the homograft was more prolonged in this patient than in the preceding 2 patients. Clinical response was rapid and dramatic; the patient was extremely pleased postoperatively because the tingling in the extremities ceased. This occurred despite a serum calcium level ranging from 6.0 to 6.4 milligrams per 100 milliliters. It would seem plausible that, after 18 years with a serum calcium of 5 milligrams per 100 milliliters or less, she might be asymptomatic with a serum calcium of much less than 9 or 10 milligrams per 100 milliliters.

CASE 4. A 51 year old female was first admitted to Piedmont Hospital in January 1960. In September 1955 she had had a subtotal thyroidectomy for nontoxic nodular goiter. Postoperatively stridor and signs and symptoms of hypothyroidism and hypoparathyroidism developed. There was difficulty in maintaining the patient on a medical regimen because the hypoparathyroid state was quite labile. Serum calcium values ranged from 7.6 to 14.0 milligrams per 100 milliliters during the course of medical treatment from 1955 to 1960. She had occasional episodes of tetany and tingling in the face and extremities. The patient was being maintained relatively asymptomatically during the 6 months preceding transplantation. However, she required 16 grams of calcium lactate (32 tablets), 100,000 units of vitamin D, 1.5 cubic centimeters of A.T. 10, and 5 grains of desiccated thyroid per day. In addition, she was on a strict low dairy product diet. The patient calculated that these medications cost approximately 400 dollars per year.

At the time of her admission the serum calcium was 7.6 milligrams, and the phosphorus was 5.6 milligrams per 100 milliliters. On 8 January 1960 thyroid tissue only that was taken from an adult female having a subtotal thyroidectomy for nontoxic diffuse goiter was homografted into the abdominal wall of the patient. Postoperatively the serum calcium has ranged from 8.6 to 10.0 milligrams, and the serum phosphorus has ranged from 4.3 to 5.3 milligrams per 100 milliliters. On 20 June 1960 the serum calcium was 10.0 milligrams, and the phosphorus was 4.5 milligrams per 100 milliliters. The serum protein bound iodine was 3.4 micrograms per 100 milliliters. Medications were decreased progressively postoperatively. A.T. 10 was discontinued immediately after homotransplantation, and calcium lactate and vitamin D were discontinued 8 weeks postoperatively. The patient has been maintained on 2 grains of desiccated thyroid per day since homografting. Uptake of radioactive iodine over the site of abdominal transplant 3 months after homografting was 9 per cent; uptake over the neck was 6 per cent.

This patient has not had an episode of tetany since homotransplantation. It had been demonstrated repeatedly preoperatively that it was not possible to maintain this patient asymptomatically without the large doses of medication stated.

Histologic studies of the tissue transplanted in this patient showed that the donor tissue had been involved by Hashimoto's thyroiditis. Throughout the thyroid gland there was an increase in fibrous tissue, and there were numerous lymph follicles, some with large, active germinal centers.

CASE 5. A 35 year old male was first admitted to Piedmont Hospital in October 1959. In 1949 he had had a subtotal thyroidectomy for toxic goiter. Postoperatively stridor and signs and symptoms of hypoparathyroidism developed. The patient was maintained with difficulty on a medical regimen. He had frequent episodes of tetany and began to take calcium lactate tablets continually. In the 5 months prior to homotransplantation of endocrine tissue it was necessary to hospitalize the patient 3 times because of frequent episodes of tetany and continual cramping pain in the extremities. During this time the serum calcium ranged from 6.6 to 8.4 milligrams and the phosphorus from 5.3 to 7.6 milligrams per 100 milliliters. In September 1959 the patient was diagnosed as having a psychoneurotic depressive reaction.

On 15 October 1959 thyroid tissue only that was removed from an adult female having a subtotal thyroidectomy for nontoxic nodular goiter was homografted into the abdominal wall of the patient. On the fifth postoperative day the serum calcium was 9.0 milligrams, and the phosphorus was 5.0 milligrams per 100 milliliters. On the twenty-first postoperative day the uptake of radioactive iodine over the site of abdominal transplant was 2 per cent; uptake over the neck was 16 per cent. Medications were decreased progressively after operation and were discontinued on the twenty-eighth postoperative day. Two months after operation, on 9 December 1959, the serum calcium was 9.5 milligrams, and the phosphorus was 3.7 milligrams per 100 milliliters. From that time until 20 January 1960 the patient was lost to follow-up. The patient was admitted to another hospital on 20 January 1960 with signs and symptoms of hypoparathyroidism; the serum calcium at this time was 7.9 milligrams, and the phosphorus was 5.8 milligrams per 100 milliliters. No further information has been received about this patient.

There was a definite, demonstrable, beneficial response of the hypoparathyroid state to the thyroid transplant in this patient. This effect lasted only 2 to 3 months, however, and the patient again had signs and symptoms of hypoparathyroidism. This was the only 1 of 5 transplants in the 4 adult patients that did not result in an increased radioactive iodine uptake over the site of abdominal transplant. This man was the only one of these patients who was not hypothyroid, which may account for this finding.

Simpson, Green and Swanson, and Robinson and associates have reported the association of hypoparathyroidism and personality changes. This patient is emotion-

TABLE I.—HOMOGRAFTS IN PATIENTS WITH ENDOCRINE DEFICIENCIES

Case No., Age, Transplant date	*Diagnosis*	*Blood type patient*	*Blood type donor*	*Donor tissue*	*Results*
1 3 months 12-8-59	Idiopathic hypoparathyroidism	A−	O+	Adult thyroid and parathyroid; nontoxic nodular goiter	Asymptomatic without medication
2 57 years 4-30-58	Postoperative hypothyroidism and hypoparathyroidism since June 1955	A+		5 mos. fetal thyroid and parathyroid	Questionable benefits for 1 month
7-20-58				5 mos. fetal thyroid and parathyroid	Asymptomatic without medication 14 mos.
9-23-59			O+	Adult thyroid and parathyroid; nodular hyperplasia of thyroid	Definite response; asymptomatic without medication for 35 days
12-3-59			B+	Adult thyroid; nontoxic nodular goiter	Asymptomatic without medication
3 59 years 1-18-60	Postoperative hypothyroidism and hypoparathyroidism since 1942	O+	O+	Adult thyroid and parathyroid; nontoxic diffuse goiter	Asymptomatic without medication for hypoparathyroidism
4 51 years 1-8-60	Postoperative hypothyroidism and hypoparathyroidism since September 1955	A+	O+	Adult thyroid; Hashimoto's thyroiditis	Asymptomatic without medication for hypoparathyroidism
5 35 years 10-15-59	Postoperative hypoparathyroidism since 1949	O−	O+	Adult thyroid; nodular hyperplasia of thyroid	Definite response; asymptomatic without medication for 2 to 3 mos.

ally unstable, and it has been very difficult to follow him up. In the Piedmont Hospital outpatient clinic we have been following up another hypoparathyroid patient who has personality changes so marked that we have been hesitant to homograft endocrine tissue.

DISCUSSION

A summary of the results of homografting in these patients is seen in Table I. The results of treatment of these patients are good. These results are similar to those reported by many others who have homografted parathyroid-thyroid tissue into endocrine-deficient patients. There is no correlation between the type of tissue transplanted and the duration of response of the patient. Three patients with hypoparathyroidism have had excellent responses to transplants of thyroid tissue only. The donor tissue in one of these patients was involved by Hashimoto's thyroiditis. The patient in Case 2 had a prolonged beneficial response to 1 of 2 fetal tissue homografts and to 1 of 2 adult tissue homografts. This lack of correlation between clinical response and type of tissue transplanted indicates that the mechanism of action is one other than survival of homografted tissue. Even if thyroid tissue did survive homotransplantation and secreted thyroid hormone, this would not account for improvement of hypoparathyroidism in these patients.

A possible explanation of the action of these transplants is that they stimulate tissues in recipient patients to produce thyroid and parathyroid hormone. Filatov and Verbitska, Engley and associates, Cordaro, and Rogers have written about "growth-promoting" factors or "biogenic stimulators." "Tissue therapy," introduced originally by Filatov, consists of implanting or transplanting preserved homologous or heterologous tissues. Filatov postulated that growth-promoting factors were produced as tissue became necrotic after removal from an organism. These biogenic stimulators were used to promote the healing of various lesions and disorders. The homologous transplants which the patients in this series

have received differ from tissue therapy only in that these transplants were not preserved. However, these transplants undoubtedly elicit a homograft response and undergo necrosis and subsequent resorption.

Schatten and co-workers reported previously a patient with squamous cell carcinoma who had a syndrome resembling hyperparathyroidism; primary hyperparathyroidism and bone destruction by tumor were excluded. There was a direct relationship between the presence of carcinoma and hypercalcemia in that patient; hypercalcemia occurred only when there was a large amount of carcinoma present. A large proportion of that carcinoma was necrotic. It is of interest that necrosis of tissue is the common denominator in that patient with carcinoma and hypercalcemia and in the patients with endocrine homografts in this series whose serum calcium increased to normal values. Connor and associates, Myers, and Plimpton and Gellhorn have reported 14 other patients with unexplained hypercalcemia associated with carcinoma. It may be of related interest that there have been reports of 27 patients with unexplained hypoglycemia associated with extrapancreatic tumors. These have all been extremely large tumors in the thorax or abdominal cavity and undoubtedly significant proportions of these tumors have been necrotic. August and Hiatt have reviewed recently the reports of nonpancreatic tumors associated with hypoglycemia. Whatever the mechanism of the stimulus evoked by transplanted endocrine tissue per se, it is of limited duration because necrotic tissue is soon resorbed after homograft reaction. The immunologic response to transplanted foreign tissue or to substances produced by breakdown of this tissue might persist for a longer time.

Witebsky and co-workers (16) have demonstrated organ-specific thyroid antibodies and an accompanying thyroiditis in rabbits after the intradermal injection of extracts of autogenous or homogenous thyroid glands combined with Freund adjuvants. Witebsky (15) found that the correlation between circulating antibodies and histologic changes in thyroid glands of dogs given extracts of homologous thyroid tissues was not as marked as it was in rabbits. However, extracts of autogenous thyroid in dogs proved to be antigenic for the individual animal itself. The serum of some patients with chronic noninfectious thyroiditis has been shown to contain a factor that reacts with human thyroid extract, and it has been proposed by Roitt and Doniach that the pathogenesis of chronic thyroiditis is related to autoimmunization.

There has been no evidence of thyroiditis in any of the patients in this series who received homografts of adult thyroid tissue. The development of circulating antibodies and histologic changes in the thyroid glands of the recipient patients were not studied.

In 3 of the 4 adult patients there has been a persistent elevated uptake of radioactive iodine over the site of abdominal transplant. However, this was not correlated with response of the patient or histologic survival of the transplant. The patient in Case 2 became markedly hypothyroid 5 weeks after her first homograft of adult tissue, despite a radioactive iodine uptake of 13 per cent over her abdomen. Also, there was no histologic evidence of thyroid tissue when a block excision of this site of transplant was performed. In the patient in Case 5, in whom there was not an appreciable radioactive iodine uptake over the abdominal site of transplant, signs and symptoms of hypoparathyroidism responded as rapidly to the transplant as occurred in the other patients. These results suggest that in hypothyroid patients the transplants, the operative procedure of transplantation, or both produce a change in surrounding tissues so that radioactive iodine is taken up but thyroid hormone is not produced by these tissues.

It is difficult to understand the reason symptoms of their disease suddenly developed in some of the patents after their having been asymptomatic without medication

for long periods after transplantation. Available evidence does not warrant a final conclusion as to the mechanism of action of thyroid-parathyroid homografts in these endocrine-deficient patients. Local tissue reaction at the site of transplant in all patients and inability to identify transplanted tissue histologically 10 weeks after implantation in 1 patient indicate that homografted tissue in these patients did not survive. This is interpreted to mean that these transplanted foreign tissues evoked well defined homograft reactions, and the problem of tissue homografting has not been solved. This fact does not invalidate in any way the demonstrable clinical and laboratory responses that occurred. There has been a tendency in the past to disregard reports of clinical improvement that follows homografts in some endocrine-deficient patients because there has not been histologic proof of survival of homografted tissues. It is suggested that good clinical results can be obtained in the treatment of thyroid-parathyroid deficient patients without prolonged survival of tissue homografts. An immunologic response to the homograft or to the substance produced during necrosis of the homograft may even be necessary to effect a good result. It is emphasized that in this study, good results were obtained when no attempt was made to use less antigenic fetal tissue, and thyroid tissue only was transplanted to hypoparathyroid patients in 3 of 6 instances.

SUMMARY

Studies are presented on 5 patients who were hypothyroid or hypoparathyroid, or both and who have received homografts of adult endocrine tissues. The clinical and laboratory responses to treatment in these patients are good. It is suggested that the beneficial effects of the homografts were not the result of prolonged survival and that necrosis of the transplants may even be a requisite.

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TWENTY-FOUR YEARS OF EXPERIENCE WITH ELECTIVE GASTRIC RESECTION FOR DUODENAL ULCER

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AT THE MEETING of the American Surgical Association in 1956, following the reports on the results of gastric surgery, Allen O. Whipple said, "In the past I have been very confused about this problem of surgery for peptic ulcer. I regret to say that after this morning's discussion I am even more confused" (3). I shared his confusion and resolved not to publicize our results until enough patients had been followed up for a long enough period to justify drawing conclusions from personal experience in the aspects of partial gastrectomy for duodenal ulcer that lead to the most controversy.

This report covers 1,488 patients who underwent elective partial gastrectomy for duodenal ulcers, with or without accompanying gastric ulcers, during the years 1936 to 1957 inclusive. Their follow-up status is reported as of 1959. Twenty-four of the 1,488 died in the hospital after operation. The number of patients who left the hospital after operation was 1,464. They have been divided into four groups; viz., those operated on during 1936 to 1945, 1946 to 1948, 1949 to 1953, and 1954 to 1957. Nearly all (98 per cent) of the first group underwent Polya or Balfour modifications of the Billroth II type of resection, the extent of resection usually not exceeding 50 per cent. The second group was similar, except that 14 per cent of these patients underwent Polya resections and 86 per cent, Hofmeister resections. The third group all underwent Hofmeister procedures and were operated on during the years when resection of at least two-thirds to three-fourths of the stomach was the objective. Toward the end of this period, 35 patients underwent vagectomy at the time of gastrectomy, but the gastrectomies were still performed high. The fourth period is marked by an increasing return to resections of 50 per cent or less in extent and by the performance of vagectomies more frequently with the resections and, occasionally, of Billroth I anastomoses. The record of the follow-up study is given in Table I. As of early 1960, a little under 4 per cent of the patients had been lost to follow-up, varying from 6 per cent of the early patients to about 2 per cent of the recent ones. The remainder had been followed up to their death or into 1959 or 1960 (a small proportion only into the latter part of 1958).

A comparison of the results of treatment of the four groups is given in subsequent tables, using as nearly as possible the same criteria for all, except, of course, the length of time the patients have been followed up. This item loses much of its significance after 6 years. Among patients who are carefully followed up, few marginal ulcers become apparent for the first time after 6 years. Most of the significant changes in weight after operation are also manifest by this time, except that patients frequently become leaner toward the end of the seventh and early part of the eighth decades. The pattern of dumping is also pretty well established by 6 years after operation. The figures presented show: (1) the postoperative (hospital) death rate, (2) the late death rate, (3) the effect of the type of anastomosis, of the extent of the resection, and of vagectomy upon the incidence of marginal ulcers and upon dumping and nutrition, (4) the clinical appraisal.

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TABLE I.—FOLLOW-UP RECORD OF ALL PATIENTS WHO HAD ELECTIVE PARTIAL GASTRECTOMY FOR DUODENAL ULCER FROM 1936 TO 1957

	Years of operation			
	1936 to 1945	*1946 to 1948*	*1949 to 1953*	*1954 to 1957*
Patients who survived operation.	296	192	506	470
Postoperative deaths in hospital.....	12(4)	1(0.5)	5(1)	6(1.3)
Died since leaving hospital.....	74(25)	34(17.7)	50(9.9)	28(5.9)
Still actively followed in 1959, 1960*.....	204	149	441	434
Duration of follow-up, yrs.....	13 to 23	10 to 13	5 to 10	1 to 5
Patients lost to follow-up.....	18(6.1)	9(4.7)	15(3.0)	8(1.7)
Average follow-up of lost patients, yrs.	8	6	3.5	0.5

*A few not contacted since late 1958.
Figures in parentheses are percentages.

POSTOPERATIVE DEATH RATE

The rates for the four groups of patients appear in Table I. In the 129 patients who had vagectomies there were no hospital deaths. Of the 43 patients with Billroth I anastomoses, 1 died in the hospital. Until 1945 the death rate was 4 per cent. For the past 15 years it has been about 1 per cent. The improvement is probably chiefly the result of the benefits to surgery that accrued during the Second World War, notably better anesthesia, early ambulation, freer use of transfusions, and antibiotics. The addition of vagectomy to resection has not added to the death rate. The improvement in the postoperative death rate is one of the two substantial advances made in surgery during the years of our study, the other being the reduction of the incidence of marginal ulcers following the addition of vagectomy to partial gastrectomy. The death rate probably can be further reduced, because approximately half the deaths which followed elective resections were the result of surgical errors or mishaps that occurred in relation to difficult dissection around the duodenum and head of the pancreas. Such dissections can be avoided by more frequent use of Bancroft type resections.

LATE DEATHS

The main points of interest among patients who died after leaving the hospital are how many of them died as a result of operation or ulcer, and what effect did gastrectomy have on longevity? Regarding the latter question, The Equitable Life Assurance Society kindly analyzed the deaths that have occurred among 296 patients who were operated on during the period 1936 through 1945. They write, "The results indicate that the mortality of those who survived their operations by at least 2 months was not significantly different from that of the general population of the United States of the same age, sex, and color during the years 1949 to 1951. This should not be interpreted to mean that those who have had gastric resections have as good life expectancies as do persons generally in good health; the population of the United States used as a standard of comparison contains individuals running through the full spectrum of healthiness, from exceptional vigor to extreme debility, at any moment." Their study further shows that the deaths among the 296 patients as of the 1958 anniversary of their operation numbered 72 as compared to 63.99 expected deaths, a mortality ratio of 113 per cent with a probable error of 9 per cent. There is no way of knowing how the health of our patients, aside from the ulcer, compared with the health of the general population, but this study does not suggest that the loss of about half of the stomach causes an individual to die significantly earlier than he would have, had the stomach been retained whole. Final proof of the effect of hemigastrectomy on longevity is still lacking.

Table I shows the number of patients who have died after leaving the hospital. The stated cause of death in all but a few instances has been obtained. All deaths seem to be unrelated to ulcer disease or the effects of operation, except in the case of 10 patients, whose deaths were attributed to the following causes: a single fatal gastrointestinal hemorrhage complicating acute

alcoholism, without other evidence of marginal ulcer (1 patient); after operation for marginal ulcer (2 patients); late surgical complications following the initial gastric resection (3 patients); marginal ulcer without secondary operation (2 patients); pulmonary tuberculosis that early followed gastrectomy (2 patients). Eight of the deaths occurred in the group of 296 patients operated upon prior to 1946. Among 1,182 patients operated on since 1946, only 2 late deaths seem possibly to be directly related to the gastrectomy, the anesthesia, or to ulcer recurrence.

MARGINAL ULCERS

It is sometimes hard to make a definite diagnosis of marginal ulcer. Roentgenograms are unreliable. Marginal ulcer was considered present if it was seen at operation, if after discharge from the hospital the patient bled (unless the source was shown to be a lesion other than ulcer), or if the patient complained of abdominal pain of a type that suggested ulcer over a period of at least 2 weeks. The patients who complained of pain but in whom no objective evidence of ulcer could be found gave the most trouble in diagnosis.

Table II gives the rate of incidence of marginal ulcers in patients with gastrectomies alone and in those who had gastrectomies plus vagectomies (or attempted vagectomies). Both are given in relation to the size of the resections as indicated by the length in centimeters of the resected specimens along the greater curvature. The most important finding in this table develops from a comparison of the patients operated on prior to 1949 with those operated on in the period between 1949 and 1953. In the earlier years, the extent of the resections, as previously reported (1) was commonly of the order of 50 per cent; during the period between 1949 and 1953 an effort was commonly made to achieve high resections and to remove at least two-thirds to three-fourths of the stomach. The measurements of nearly 80 per cent of the resected specimens during that period were in the middle and larger groups, whereas previously over 70 per cent had been in the middle and smaller groups. There was no substantial change in the rate of recurrent ulcers, whatever the extent of resection, until vagectomies were added to resections in 1952. This experience runs counter to a widely held belief that the removal of more of the stomach gives the patient a better chance of avoiding recurrent ulcer. Perhaps outside the range of 40 to 75 per cent resections, that observation is true, but within that range in my experience it did not hold. Furthermore, within that range, a detriment to nutrition demonstrably followed the higher resections. Vagectomy gave better protection against recurrent ulcers than did high resections and did not adversely affect the nutrition. The better showing made by the group who had vagectomies is not simply a matter of a shorter follow-up period, because in those patients who had resections without vagectomy during the same years a substantially greater number of marginal ulcers have already developed. Incidentally, the 3 patients for whom vagectomy was attempted but in whom marginal ulcers developed all showed free hydrochloric acid by the Hol-

TABLE II.—RECURRENT (MARGINAL) ULCERS FOLLOWING PARTIAL GASTRECTOMY FOR DUODENAL ULCER

	Years of operation				
	1936 to 1945	*1946 to 1948*	*1949 to 1953*	*1954 to 1957*	*1952 to 1957*
No. of patients	296	192	471	349	156
Vagectomy	No	No	No	No	Yes
Type of anastomosis, per cent					
Polya	98	14			
Hofmeister		86	100		
Varied				Yes	Yes
Length of specimen along greater curvature, per cent					
0–18 cm.	43	42	21	32	46
19–23 cm.	28	30	35	39	35
24 cm. plus	28	27	44	27	19
Unknown	1	1	—	2	1
Usual size of resection, per cent	50	50	67–75	Varied	Varied
Marginal ulcer rate, per cent	7.8	10	8.1	7.1	2.6

TABLE III.—RESULTS OF TREATMENT OF MARGINAL ULCERS

	Conservative treatment	*Thoracic vagectomy*	*Other operations*
Died after operation	—	2*	2
No further symptoms	42	27	7
Return of ulcer	3	2†	1
Other symptoms	13	3	3
Lost to follow-up	3	—	—

*Both deaths caused by disease concomitant to ulcer.
†One had multiple endocrine tumors. One still bleeds at times from no obvious source.

TABLE IV.—INCIDENCE AND SEVERITY OF DUMPING

	Years of operation		
	1936–1948	*1949–1953*	*1954–1957*
No. of patients	488	506	470
Usual extent of resection, per cent	50	67–75	60–75*
No record about dumping, per cent	7.6	6.1	6.2
Dumping, Grade I, per cent	11.5	19.4	25.6
Dumping, Grade II, per cent	2.4	5.3	4.1
Dumping, Grade III, per cent	1.1	2.5	2.2

Percentages are based on number of patients whose records of dumping were obtained.
Although the incidence and severity of dumping cannot be exactly recorded, this table fairly represents the clinical extent of the problem.
*For 80 per cent of the patients; 50 per cent resection for the other 20 per cent.

TABLE V.—COMPARISON OF POSTOPERATIVE WEIGHTS TO PREOPERATIVE WEIGHTS

	Years of operation		
	1936–1948	*1949–1953*	*1954–1957*
No. of patients	488	506	470
Estimated size of usual resection, per cent	50	67–75	60–75*
Gained weight	343(70)	249(49)	213(45)
Lost weight	126	243	244
Lost with excuse†	70	94	93
Lost without excuse	56(11)	149(29)	151(32)
Record incomplete	19	14	13

*For 80 per cent of the patients; 50 per cent resection for the other 20 per cent.
†Excused were those patients who (a) after 3 to 5 years gained over their preoperative weight, or (b) remained of average weight for their age, height, and sex even though they lost after operation, or (c) had a severe disease other than ulcer to explain their weight loss, or (d) were over 70 years old at operation.
Figures in parentheses are percentages.

lander test after the operation, suggesting that the vagectomy was actually not accomplished. It further appears in Table II that the marginal ulcer rate prior to 1946, when Polya modifications of Billroth II resections were almost exclusively used, is about the same as in the later years when Hofmeister resections were the rule. This comparison is especially valid between the two groups performed prior to 1949, when the resections were substantially the same in extent and whose period of follow-up is similar. The type of anastomosis had no demonstrable bearing on the rate of marginal ulcers. There were not enough Billroth I anastomoses without accompanying vagectomies to include them in this statement.

There were 108 marginal ulcers in all. Four patients have died of the ulcer, 2 of these after secondary operations for the ulcer in the days before vagectomy. Sixty-one patients were treated conservatively and 34 by thoracic vagectomy. These are the two methods now preferred, using whichever seems best for each patient. The status of the 108 patients after treatment appears in Table III. The 2 patients who were not benefited by thoracic vagectomy consisted of 1 who had a proved endocrine adenomatosis syndrome who finally underwent a total gastrectomy, and 1 who bled mildly at times for no apparent cause.

With few exceptions, the marginal ulcers have given obvious symptoms within 6 years after the gastric resection. The few that have been first discovered later than 6 years after operation have often been associated with alcoholism.

DUMPING AND NUTRITION

By dumping is meant a clinical symptom-complex, not just a roentgenographic finding of rapid emptying. Recently nearly all patients who are still living have been asked whether they had faintness or sweating shortly after meals, and if so, whether it happened often or was severe. Occasionally they will answer no, but that they experience weakness, desire to lie down, palpitation, flushing, nausea, or sense of uncomfortable fullness. It is hard to distinguish dumping symptoms from those caused by small gastric capacity. When equivocal, any postprandial symptoms have been attributed to dumping. Three degrees of severity of dumping have been set up; viz., grade I comprises patients whose symptoms occur only occasionally and are seldom severe; grade II includes patients who every day have to take precautions against dumping (such as omitting breakfast) but who undergo little more than annoyance if they follow

their regimen; and grade III includes patients who dump in spite of taking precautions and whose symptoms are severe and even incapacitating. Dumping symptoms tend to improve with time. Those that disappeared after about a year were not recorded.

Table IV shows the incidence of dumping in the series. In the years 1936 to 1948, when approximately 50 per cent resections were performed, the incidence of all grades of dumping was lowest. Although dumping existed in those days more frequently than was realized, it was rarely severe. In recent years, 50 per cent resections are again being performed more and more, and among these patients the incidence of severe dumping has again declined to less than 2 per cent. The highest incidence occurred during the years when high resections were regularly performed. Among patients whose resections are not over 50 per cent, the incidence of serious dumping has consistently been low, regardless of the type of anastomosis or size of stoma that was employed. There was no attempt to make very small stomas. The incidence of all grades of dumping has clearly been higher among psychologically unstable patients than among stable ones. The severe dumper is a problem indeed in management, but the problem does not persist often enough for changes to be introduced in the present method of operation. The detection before operation of patients who are likely to dump may be desirable and lead to special operative treatment in their case.

Nutrition is the most difficult of the results of partial gastrectomy to appraise and the one that has led to the most confusion among the reports in the literature. The chief purpose of studying nutrition has been to discover which patients, because of poor nutrition, were either harmed or not benefited by gastrectomy. The records have been examined with four questions in mind; viz., did the patient gain or lose as compared with his best weight recorded in the hospital chart at the time of admission before operation, how much in pounds did he gain or lose, did his weight consistently remain more than 5 per cent below its preoperative figure, how did his weight compare with the average for his height, age, and sex both before and after operation? None of these criteria alone is sufficient but together they serve their purpose. The table of averages used is that compiled by the Equitable Life Assurance Society of the United States during 1940. This table does not include those over the age of 45, but this age was used for the many patients over 45 in this series. The tables published by Master, Lasser, and Beckman indicate that more of the older patients should have been considered near to average than were recorded. To permit comparisons the patient's weight has been taken at 3 to 5 years after operation, and, as far as possible, only weights have been used that were maintained.

Table V shows how the patients fared regarding gain or loss after operation. A comparison of the two columns headed 1936 to 1948 and 1949 to 1953 best reveals the ill effect of high resections upon the

TABLE VI.—COMPARISON OF PATIENTS' WEIGHTS AFTER OPERATION WITH TABLE OF AVERAGE WEIGHTS

	Years of operation		
	1936–1948	*1949–1953*	*1954–1957*
No. of patients	488	506	470
Patients with records complete	357	431	437
Usual size of resection, per cent	50	67–75	60–75*
Satisfactory weight	315(88)	363(84)	355(81)
No. of patients 20 to 25 per cent below average weight			
Before operation	46	39	27
After operation	24	24	45
No. of patients lighter than 25 per cent below average weight			
Before operation	46(12.9)	35(8.1)	40(9.1)
After operation	18	44	37
Excused for low weight†	5	16	14
Without excuse	13(3.7)	28(6.5)	23(5.3)

*For 80 per cent of the patients; 50 per cent resection for the other 20 per cent.
†Excused are patients who had severe disease other than ulcer, or were over 70 years old at operation.
Figures in parentheses are percentages.
Percentages are based on number of patients whose record is complete.

TABLE VII.—PATIENTS WHOSE COURSE WAS NOT THOROUGHLY SATISFACTORY

	Years of operation		
	1936–1948	1949–1953	1954–1957
Marginal ulcers, per cent...	8.6	7.5	6.0
Late severe surgical complications, per cent.....	1.2	0.5	0.5
Severe dumping, per cent..	1.1	2.7	2.1
Moderately severe dumping, per cent.....	2.4	5.3	4.1
Possibly harmful weight loss			
With symptoms,* per cent	1.7	3.0	3.4
Without symptoms,† per cent.....	1.7	4.4	4.3
Gained, but still low in weight			
With symptoms, per cent	0.8	0.6	0.5
Without symptoms, per cent.....	5.0	3.5	3.9
Lost 10 per cent of preoperative weight but still satisfactory weight for height			
With symptoms, per cent.....	0.8	1.9	1.6
Without symptoms, per cent.....	2.2	4.9	4.3

*The symptoms referred to are chiefly mild dumping or inability to eat a big meal.

†Statistical Bulletin of the Metropolitan Life Insurance Company, Volume 40, November-December 1959, page 3, contains Table 2—Desirable Weights For Men and Women According to Height and Frame, Ages 25 and Over. According to this table, some weights of even 25 per cent below the figures that we have taken as average, are desirable, notably for short women of small frame. Their table includes few of our average weights as being desirable. Classification of patients as being not thoroughly satisfactory merely because their weight is low may not be justified.

Patients are not included in this table if their course is too complicated to appraise because of severe disease that is not related to their ulcer or the effects of their operation.

patients' ability to gain weight after operation.

In Table VI the weight of the patients is compared with the average weight for the same age, sex, and height. The most significant lines are the bottom four that show how few patients with 50 per cent resections stayed in or entered into the lowest weight class after operation, compared with the patients who had higher resections, in spite of the fact that this relationship was reversed before operation. No factor in operative technique has been as consistent in its effect on the patients' weight as the amount of the stomach removed. The record is incomplete for about 16 per cent of the patients, largely because the height of many of the patients who died after leaving the hospital is not known. Life insurance companies do not impose higher rates than usual on applicants for insurance solely because their weight is below average, unless the degree below average exceeds 25 per cent, since people who weigh 1 to 25 per cent below average apparently live as long as people whose weight is average, unless some disease is present that causes the low weight. Table VI records the number of patients who were 20 to 25 per cent below average, in order to show how many were close to the critical 25 per cent limit and also how many were below the limit.

The patients who were always heavier than 20 per cent below average present clinically no significant nutritional problems. Even those weighing 20 to 25 per cent below average seem, with few exceptions, to be little harmed. Thirteen of the 93 in this group complained of dumping or inability to eat a big meal. One complained of weakness. The others were essentially free of complaints, although several wanted to be able to put on weight. Of this group, 43 patients, nearly half, were in the same weight group or thinner before operation. Of the 99 patients who were lighter than 25 per cent below average after operation, 53 were so before operation, and 15 others were in the 20 to 25 per cent below average group before operation. In other words, people with ulcers who are lean before operation are often still lean after the operation. Sixty-four of the 99 had no serious illness other than ulcer to explain their low weight, but 27 of these 64 had complaints after operation, chiefly inability to eat full meals and dumping. It is significant that of the 1,225 patients whose records include their height, only 15 patients (1.2 per cent) got into the class of more than 25 per cent below average because they lost 10 pounds or more when no reason for weight loss other than operation (such as severe illness) was present. Only 1 of these 15 patients was among the group operated on prior to 1949, when relatively small resections were being performed. Over half of them were operated on after 1953 and may yet gain. Most of them were women. Nearly all apparently had resections of over 50 per cent. The same

statements hold for those who were in the 20 to 25 per cent below average weight group because of losing 10 pounds or more, except that they numbered 2 per cent. Taking both of these groups together, 1 patient among them had a marginal ulcer, 3 tire easily or feel weak, 2 have severe dumping, but the remainder have no symptoms, or mild ones, such as inability to eat full meals or mild dumping. Harmful loss of weight because of the operation has not occurred often, in our experience, especially when resections are kept below 50 per cent.

The tabulation of the number of pounds gained and lost after operation and of the number of patients who consistently remained 5 per cent or more below their preoperative weight is not given here. It throws little light on the nutritional aftereffects of the resections.

TABLE VIII.—COMPARISON OF 1960 WEIGHT RECORDS OF PATIENTS WITH BILLROTH I AND BILLROTH II ANASTOMOSES PERFORMED 1953 TO 1958

	50 per cent Resections, Billroth II for duodenal ulcer	*All Resections, Billroth I for peptic ulcer*	*50 per cent Resections, Billroth I for duodenal ulcer*
No. of patients	134	133	68†
Lost weight	71	57	30
Lost, with excuse*	36	29	18
Lost, without excuse	35(26)	28(21)	12(18)
Lost, to become 20–25 per cent below average	4(3)	9(7)	5(7)
Gained, but still 20–25 per cent below average	5(4)	6(5)	4(6)
Lost, to become or remain lighter than 25 per cent below average	1(1)	4(3)	3(4)
Gained, but still lighter than 25 per cent below average	1(1)	4(3)	3(4)

*See Table VI for list of excuses.
†Three patients not heard from.
Figures in parentheses are percentages.

CLINICAL APPRAISAL

In Table VII are included all the patients who did not have a thoroughly satisfactory result from the operation. The degree of dissatisfaction diminishes from the top items toward the bottom. This table is perhaps an exhibition of leaning over backward. Actually, the patients labeled unsatisfactory without qualification in our own minds are found only among four groups, viz., those who had marginal ulcers, late severe surgical complications, severe persistent dumping, or harmful weight loss with symptoms. Even for most of these patients, the operation did more good than ill. The majority of the patients who had marginal ulcers are now free of symptoms. Of the 28 patients with severe dumping, 22 maintain a good weight, are working, and eat a liberal diet without symptoms of ulcer. Only 4 of the patients with moderate (grade II) dumping are in the low weight groups. Between the clearly satisfactory and unsatisfactory results, gradations exist. Similarly, low weight is not a reliable criterion for classifying operative results. If a patient in his seventies is still working, has gained weight, and denies symptoms, his condition cannot be considered unsatisfactory even if his weight remains low. Twenty-seven patients (2.3 per cent), who are not unsatisfactory because of marginal ulcers or severe dumping but who have symptoms (such as inability to eat a full meal), have lost weight since operation and have remained in the lower weight group. These could be called unsatisfactory on a nutritional basis, although nearly half of them were operated on since 1954 and may yet gain.

EFFECT OF TYPE OF ANASTOMOSIS UPON THE CLINICAL COURSE

Our records show little to choose between Polya and Hofmeister anastomoses except that the former, commonly performed with low resections, were followed by the least incidence of persistent severe dumping (2 of 549 patients). Controversy centers upon the question of whether the Billroth I anastomosis offers advantages over the Billroth II types. In the matters of immediate postoperative complications, incidence and severity of late dumping, and marginal ulcers, surely no advantage in the Billroth I was noted. The record of the nutritional results is seen in Table VIII in which all patients who underwent Billroth II procedures, 50 per cent in extent, are compared

with all those who underwent Billroth I resections for any peptic ulcer during the same period, and with the patients among these whose Billroth I procedures were performed solely for duodenal ulcers, and accompanied by 50 per cent resections or less. Fewer of the patients with the Billroth I technique lost weight without excuse than their counterparts with the Billroth II, but the losses suffered by the Billroth I patients were more often serious. So far, there is little to choose between them, certainly not enough to justify the performance of one procedure over the other if it is not the easy, natural way to treat the ulcer at hand. Any Billroth II procedure has the great advantage of permitting safe management of difficult duodenal or pyloric ulcers by means of a modified Bancroft-type technique. The 202 patients in this table who were operated on for duodenal ulcer already have a better nutritional record than the patients who had more than 50 per cent resections who were operated on in previous years.

DISCUSSION

The most important advance witnessed during 24 years of operations for duodenal ulcer is the maintenance for the past 14 years of a hospital mortality of about 1 per cent for elective partial gastrectomy. This is not the result of selection of cases. Very few less extensive procedures, such as gastroenterostomies, have been performed during these years. The incidence of marginal ulcers can apparently be reduced from about 8 to less than 2 per cent by adding subdiaphragmatic vagectomy to the resection. Vagectomy is well worth doing if the exposure is good but should not be attempted if the surgeon believes it would add appreciably to the operative risk. Vagectomy has rarely been linked, in our experience, with undesirable sequelae of more than minor consequence and does not appear to influence the incidence of nutritional or dumping problems for good or ill. Resections of over 40 to 50 per cent of the stomach are to be avoided. Higher resections added to the incidence of severe dumping and nutritional difficulties and did not reduce the incidence of marginal ulcers during the extensive period of trial given. Vagectomy offers surer and less harmful protection, even if for some reason it has to be performed as a second stage through the chest after the marginal ulcer has occurred. The significance of the dumping problem centers about the 1 to 2 per cent of patients who have it severely. These patients are treated individually as their complaints become evident, but it is believed that methods can be evolved for identifying them before selecting their surgical treatment. In the matter of nutrition, apparently the most important influence is the nature of the patient, i.e., the habitus, degree of psychic stability, environmental pressures, general health, and the sex. The size of the resection also controls the patient's ability to maintain weight, but other factors have relatively little influence.

SUMMARY

1. Twenty-four years' experience with elective gastric resections for duodenal ulcer is analyzed.

2. In our hands, a resection of about 40 to 50 per cent of the stomach plus a subdiaphragmatic vagectomy has given the best results.

3. A postoperative death rate of 1 per cent for such operations can be maintained.

4. The type of anastomosis that is performed is relatively unimportant provided that it can be safely employed for the ulcer at hand.

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SOME LABORATORY AND CLINICAL OBSERVATIONS ON COLY-MYCIN (COLISTIN) WITH PARTICULAR REFERENCE TO PSEUDOMONAS INFECTIONS

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SINCE THE ADVENT of the antibiotics the pseudomonas group of organisms has assumed increasing importance, because it often causes a superinfection during the antibiotic treatment of diseases caused by other organisms, particularly along the respiratory and urinary tracts. The pseudomonas has always been troublesome to the surgeon as an infective agent in operative or accidental wounds or in burns. One thinks of the pseudomonas group of organisms as surface infectors. These organisms are rarely invasive and seldom get into the blood stream unless the distributing focus is inadequately drained, but unless they can be eliminated they persist locally, delay wound healing, prevent successful skin grafting, or melt away new skin. Up to the present time the only antibiotic consistently potent against the pseudomonas has been polymyxin B which has had the handicap of nephrotoxicity when administered systemically.

During the past year laboratory and clinical observations have been made on coly-mycin, an antibiotic said to be potent against many strains of pseudomonas as well as certain other gram-negative rods and yet, reportedly, relatively nontoxic when given systemically.

Coly-mycin was discovered in Japan by Koyama in 1946 and announced in 1950 by Koyama and associates. It has been reported in the Japanese, French and Italian medical literature. Coly-mycin has been misnamed, because it is not a mycin. It is produced by the Aerobacillus colistinus. Reports indicate that it is a strong bactericidal antibiotic. It is not absorbed from the alimentary tract, but stays within the tract and acts locally on several species of the intestinal bacteria. For systemic use coly-mycin must be given intramuscularly, but it is potent locally against susceptible bacteria on body surfaces, in body cavities, and in wounds. The form prepared for intramuscular injection is sodium colistin methanesulfonate, designated as coly-mycin M. A number of preliminary reports on coly-mycin were made at the Symposium on Antibiotics in Washington in November, 1959.

This report is concerned with laboratory studies of 172 strains of pseudomonas associated with a variety of infections in several hospitals in Miami, Florida and 35 clinical patients treated with coly-mycin (colistin) either systemically or locally or both systemically and locally.[1]

IN VITRO APPRAISAL OF COLY-MYCIN

Sources of pseudomonas strains. With regard to the sources from which the cultures of pseudomonas came, the largest number of strains, 57, came from urine cultures. In most cases these represented serious urinary tract infections. The next largest number, 40, were recovered from sputum. The third largest group of strains, 28, played a role in wound infections. The rest, 47, were of

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[1]Coly-mycin S (colistin sulfate) in tablet form was used for oral administration and coly-mycin M (sodium colistin methanesulfonate) was used in solution for local and systemic administration.

TABLE I.—OTHER ORGANISMS ASSOCIATED WITH PSEUDOMONAS

Organisms	*No.*
Alpha streptococcus	45
Aerobacter (species)	37
Hemolytic Staphylococcus aureus coagulase-positive	32
Proteus (species)	23
Escherichia coli	17
Neisseria (species)	13
Micrococcus coagulase-negative	9
Other	17

TABLE II.—PSEUDOMONAS DISC SENSITIVITIES (172 STRAINS)

Antibiotic	*Sensitive*	*Moderately sensitive*	*Resistant*
Coly-mycin	149	11	12
Polymyxin	146	13	13
Neomycin	45	101	26
Streptomycin	66	25	81
Chloromycetin	11	49	112
Tetracycline	7	31	134

heterogeneous origin, notably nasopharyngeal cultures in children, tracheostomies, the umbilical cord, the external auditory canal, various abscesses, and ulcers. Only 1 culture was obtained from the blood stream.

The great majority of these organisms were recovered from polymicrobic infections. The ratio of mixed to pure cultures in the four groups mentioned is 4 to 3, 9 to 1, 4 to 1, and 2 to 1, respectively. This ratio for the entire list is 5 to 2. This fact adds greatly to the difficulty of appraising the value of any one antibiotic in the treatment of these infections.

Associated organisms in the polymicrobial cultures. Table I shows the associated organisms present in these mixed cultures. The streptococci and the neisseria were present mostly in the sputum cultures. The aerobacter, proteus, and coli were found mostly in the urine cultures. The coagulase-positive staphylococci and other micrococci, as well as the gram-negative rods, were frequently recovered from the wound cultures. These associated organisms were very often resistant to the action of coly-mycin and required the combination of some other antibiotic with the coly-mycin in order to bring the infection under control. This brought up the question of whether these antibiotics were synergistic or antagonistic to one another.

Sensitivities of the pseudomonas strains. Table II shows the sensitivities of the pseudomonas strains to 6 of the most commonly used antibiotics. Bacitracin was not listed because most pseudomonas strains are highly resistant to it. These tests were made with dilute and concentrated strength discs containing 1.66 micrograms and 10 micrograms, respectively. Strains showing inhibition by both discs were listed as sensitive; strains showing inhibition to only the concentrated disc were considered moderately sensitive; those showing no inhibition were classified as resistant. We are satisfied that disc sensitivity correlates satisfactorily with clinical effectiveness.

It is evident that coly-mycin was as good as, if not better than, polymyxin B. Chloromycetin and the tetracyclines were impotent against the great majority of the strains. Neomycin and streptomycin came somewhere in between. It was particularly interesting that neomycin showed a large proportion in the moderately sensitive group. That is, the strains were inhibited only by the concentrated disc.

Sensitivities of other gram-negative bacilli. Table III shows the effect of coly-mycin on certain other gram-negative rods found in these mixed infections and in other cases of clinical infections. This table clearly indicates that the great majority of the strains of Escherichia coli, of the aerobacter group, and of the paracolon group are susceptible or sensitive to coly-mycin. However, the great majority of the strains of proteus were resistant to coly-mycin.

THE CLINICAL APPRAISAL OF COLY-MYCIN IN THE TREATMENT OF INFECTION

It has been difficult to appraise this antibiotic, coly-mycin (colistin) clinically because of the fact that many of the infections treated were due to a mixture of organisms not all covered by any one antibiotic. Second, in many cases, treatment was begun empirically without the benefit of a previous culture study. Frequently one antibiotic after another or combinations of antibiotics

were used before the physician knew what the causative and associated organisms were. Even when cultures were taken, the physician sometimes failed to get the result from the laboratory or failed to pay attention to it when it was delivered and attached to the chart.

In this group of 35 treated patients, cultures were invariably taken before treatment with coly-mycin was started and there was definite indication for its employment. However, in some of these cases, after treatment with coly-mycin had been started, other antibiotics were added to or continued with the treatment in order to cover associated organisms.

There will always be a difference of opinion among observers regarding the result in some cases. Perhaps the difference is largely the difference between the viewpoint of the optimist and that of the pessimist. One may ask what criteria have been used in our evaluation of coly-mycin. One criterion has been the disappearance or elimination of the organism. The other criterion has been rapid or steady improvement after treatment, when there was none before. In the cases of intestinal prophylaxis a favorable result meant no growth of susceptible organisms at the site of resection.

A carefully considered appraisal was made of the clinical results obtained in the 35 patients treated with coly-mycin. There were 4 groups according to the method of administration. In 13 patients receiving systemic treatment only, the usual starting dose was 1 million units (30 milligrams) every 8 hours, but some desperately ill patients received 3 million units (90 milligrams) every 6 hours. Of these 13 patients, the results were considered favorable in 5, questionable in 5, and nil in 3. In 11 patients receiving local treatment only, 10,000 to 20,000 units (0.30 to 0.60 milligram) per cubic centimeter of solution or per gram of ointment were used, applied to the infected area once or twice a day. The results were considered favorable in 9 cases and questionable in 2. Seven patients received both

TABLE III.—SENSITIVITIES OF CERTAIN OTHER GRAM-NEGATIVE BACILLI

Organism	*Total No.*	*Sensitive*	*Moderately sensitive*	*Resistant*
Escherichia coli.....	124	106	12	6
Aerobacter species...	72	52	15	5
Paracolon species....	17	10	2	5
Proteus species.....	63	3	1	59

TABLE IV.—RESULTS ACCORDING TO CLINICAL DIAGNOSIS

Type of infection	*Total cases*	*Favorable*	*Questionable*	*No effect*
Urinary infections.....	10	3	4	3
Intestinal prep.....	4	3	1	0
Infected operative wound....	3	2	1	0
Peritoneal abscess.....	3	3	0	0
Ulcer of leg.....	3	3	0	0
Ulcer of foot.....	2	2	0	0
Osteomyelitis of ribs.....	2	2	0	0
Miscellaneous*.....	8	6	2	0
Total.....	35	24	8	3

*One case each of ulcer of the thigh, gangrene of the abdominal wall, ulcer of the face, infected burn, otitis externa and media, partial ileocolectomy, bronchopneumonia, and bronchial fistula.

systemic and local treatment, and in all of these the result was considered favorable. In 4 cases of intestinal prophylaxis, the bowel was prepared for resection by combining coly-mycin with bacitracin and neomycin. Bacitracin 40,000 units, neomycin 400 milligrams, and coly-mycin S (colistin sulfate) 1 million units (30 milligrams) were given orally in tablet form every 6 hours for 8 doses immediately before operation. In 3 of the 4 patients the bowel was free of viable susceptible organisms at the level of resection. In the fourth patient the organisms were greatly reduced in number.

In the 20 patients receiving systemic treatment, no toxicity was observed, no deleterious effect on the liver, kidney, blood, or blood-forming organs, and no alteration of the blood chemistry. The body fluids and electrolytes were not disturbed.

The results in the patients treated only systemically were not as favorable as in those treated locally or by the combined method. This may have been due to the fact that the systemic doses were too small. In 1 case, when the dose was doubled, results were obtained not seen with the smaller dose with which treatment had started. Certainly the philosophy of antibiotic treatment

is to bring the antibiotic into close contact with the bacteria in sufficient concentration and for a sufficient length of time to kill the organisms or render them incapable of multiplication. It would seem likely that with systemic coly-mycin treatment alone this objective could be better accomplished with doses of from 100 to 250 milligrams every 6 or 8 hours if it is nontoxic.

In Table IV the results are listed from the point of view of clinical diagnosis. The questionable and negative results are largely in the group of urinary tract infections. We believe that these results would have been greatly improved if a greater effort had been made to deliver the antibiotic to the region of the infection in larger dosage by both systemic and local administration.

INHIBITION OF COLY-MYCIN ACTION

As has been mentioned, the necessity of using a combination of antibiotics in mixed infections poses the problem of synergism or antagonism of the antibiotics. Some preliminary experiments have yielded interesting results, but further work must be done before these results can be reported.

One interesting side line of this study is based upon the observation of one of our laboratory technicians that when proteus and pseudomonas were present together, the proteus seemed in some way to interfere with the potency of the coly-mycin against the pseudomonas. We have confirmed this observation by showing that filtrates from 2 of 5 different strains of proteus had definite inhibiting action on the coly-mycin action with respect to 2 different strains of pseudomonas. These results are shown in Table V.

With the pseudomonas strain 1, preliminary tests indicated that the minimal inhibiting concentration of the coly-mycin was 60 units per cubic centimeter. When a series of concentrations was set up to range above and below this level, it was found that, in the control with 0.1 cubic centimeter of broth without any proteus filtrate, growth appeared in the 40 unit tube but not in the 60 unit tube. Approximately the same result was obtained with 0.1 cubic centimeter of proteus filtrate from the proteus strains 1, 4, and 5. However, 0.1 cubic centimeter of the proteus filtrate from strains 2 and 3 showed inhibition of the coly-mycin effect.

With the pseudomonas strain 2, the preliminary tests showed the minimal inhibiting concentration of coly-mycin to be between 30 and 40 units per cubic centimeter. In this test the filtrate from the proteus strain 1 gave a result similar to that in the control, but all of the other filtrates showed varying inhibition of the coly-mycin effect.

CASE REPORTS

Brief abstracts of 6 cases in our coly-mycin study series will be representative of the whole series.

CASE 1. This 68 year old woman had had a slowly spreading area of infectious gangrene on the calf of the left leg. The lesion had been treated in various ways by several physicians without benefit. One of these referred the patient to one of us (F.L.M.). At that time the lesion was of 4 months' duration and measured about 18 by 10 centimeters in diameter.

Cultures yielded a hemolytic Staphylococcus aureus, an alpha streptococcus and Pseudomonas pyocyanea. The staphylococcus and streptococcus were both susceptible to bacitracin, the staphylococcus to neomycin, and the pseudomonas to polymyxin and coly-mycin.

Bacitracin was given intramuscularly, 20,000 units every 8 hours, for 3 days and then every 12 hours for 3 more days without much benefit. After the fourth day the whole area was excised and the wound was dressed locally with nylon wet with a solution containing bacitracin, neomycin, and polymyxin. On the eighth postoperative day the wound was covered with postage stamp skin grafts. These took well, but on the third day, in spite of the continued local use of the antibiotic mixture, the pyocyaneus again manifested its presence by the appearance of green pus. Coly-mycin in a concentration of 10,000 units (0.3 milligram) per cubic centimeter was then added to the antibiotic mixture. Within 24 hours the green color disappeared and the grafted area went on to complete healing.

Coly-mycin used locally in a concentration of 10,000 units (0.3 milligram) per cubic centimeter promptly brought Pseudomonas pyocyanea under control after polymyxin had failed to do so.

TABLE V.—INHIBITION OF COLY-MYCIN ACTIVITY ON PSEUDOMONAS BY PROTEUS FILTRATE

Proteus filtrate	*Coly-mycin units per cubic centimeter*									
	120	*100*	*80*	*60*	*50*	*40*	*30*	*20*	*10*	*0*
	PSEUDOMONAS STRAIN I									
1	0	0	0	SG	—	x	—	x	—	x
2	0	x	x	x	—	x	—	x	—	x
3	x	x	x	x	—	x	—	x	—	x
4	0	0	0	SG	—	x	—	x	—	x
5	0	0	0	SG	—	x	—	x	—	x
Control	0	0	0	0	—	x	—	x	—	x
	PSEUDOMONAS STRAIN II									
1	—	—	—	0	0	0	x	x	x	x
2	—	—	—	x	x	x	x	x	x	x
3	—	—	—	x	x	x	x	x	x	x
4	—	—	—	0	x	SG	x	x	x	x
5	—	—	—	SG	SG	x	x	x	x	x
Control	—	—	—	0	0	0	x	x	x	x

x, Growth; SG, slight growth; 0, no growth.

CASE 2. This 68 year old man had his gallbladder removed in 1957. The wound became infected and the infection spread up to the ribs, sternum, and costal cartilages. He was hospitalized for 15 months, but the wound did not heal.

When admitted to Jackson Memorial Hospital in Miami, the patient had 4 discharging sinuses in the anterior chest wall. A biopsy showed infected tissue, and on the sixteenth day the infected bone and cartilage were partially removed. The wound was kept wet by frequent applications of very dilute bacitracin-neomycin solution. One month later the wound was skin grafted, but most of the grafts were lost because there was continual drainage from a number of sinuses leading down to residual infection in the bones and cartilages.

One of us (F.L.M.) was called in consultation. Cultures from the sinuses yielded Pseudomonas aeruginosa which was susceptible to both colymycin and polymyxin. Coly-mycin administration was started intramuscularly, 1 million units (30 milligrams) every 8 hours, and 3 times a day a solution containing bacitracin, neomycin, polymyxin, and coly-mycin was injected with a blunt needle into the sinuses. There was some improvement in the wound, but drainage from the sinuses persisted and bare bone could be felt at the bottom of most of the sinus tracts. When after 2 weeks of this conservative treatment it was obvious that the infection could not be controlled without radical removal of the diseased bone, this was done, and all of the infected cartilages and the involved portions of the ribs were removed. Postoperatively, the systemic administration of coly-mycin was continued as was the local application of the antibiotic mixture mentioned. Three days after this operation the patient suffered a coronary attack but he recovered. The infection in the wound cleared rapidly. Cultures taken from the wound on the eighth postoperative day failed to yield the pseudomonas. The systemic coly-mycin was discontinued after 24 days and local dosage maintained.

There was no clinical evidence of toxicity from the systemic administration of coly-mycin. The serum protein remained normal. The red blood cells, hemoglobin, and hematocrit values were below normal, both at the beginning and at the end of treatment. The white cells were unchanged. The bromsulphalein test of liver function showed 12 per cent retention after 1 hour. The cephalin flocculation test was negative. The prothrombin time was normal. The thymol turbidity test was negative.

Coly-mycin was not able to clear the pseudomonas infection until the infected cartilages and bone had been removed, as was expected. However, after these had been excised, the infection promptly came under control. There was no evidence of toxicity after the systemic administration of 72 million units (2,160 milligrams) of coly-mycin.

CASE 3. This 65 year old woman was found to have a cancer of the ascending colon. For 48 hours immediately preceding operation she was given 20,000 units of bacitracin, 200 milligrams of neomycin, and 1.5 million units (45 milligrams) of coly-mycin by mouth every 6 hours, for a total of 8 doses. There were no disturbing effects.

Cultures taken from the ileum and colon at the level of resection and from the open anastomosis showed no growth after a 48 hour incubation period. The wound healed without infection.

The bowel was rendered sterile by the preoperative treatment with bacitracin, neomycin, and coly-mycin administered orally, so that it seems fair to call the result favorable. However, this is sometimes ac-

complished with bacitracin and neomycin alone.

CASE 4. This 54 year old white male came into the hospital with a retroperitoneal abscess. It was operated upon and drained on the third hospital day. One month later a right cutaneous ureterostomy was performed.

Over a period of 2 months the patient was given erythromycin, chloromycetin, kanamycin and gantrisin, one after another, without control of the infection. A culture was taken which yielded proteus, resistant to coly-mycin, and Aerobacter klebsiella and Pseudomonas fluorescens, both susceptible to coly-mycin. Coly-mycin was given intramuscularly in a dosage of 1 million units (30 milligrams) every 6 hours and was continued for 8 days, at which time the urine had cleared and both the pseudomonas and the aerobacter had disappeared from it. However, the proteus continued, and alpha streptococcus, heat resistant, and paracolon bacilli were also cultured from the urine. These were both resistant to coly-mycin.

No toxic effects were noted on the blood, the urine, or the liver or kidney function during or after coly-mycin treatment.

This is considered a favorable result, because under treatment with coly-mycin both the pseudomonas and the aerobacter organisms disappeared from the urine and the patient was much better, in spite of the fact that other organisms were still present on culture.

CASE 5. This boy, aged 8 years, had had draining ears since he was 4 months old. At first a penicillin-resistant staphylococcus had been found, but more recently a pseudomonas had been cultured from the left ear.

On examination, there was only a slight discharge in the right ear and an intact ear drum, but on the left side there was a large opening in the drum with a large quantity of purulent discharge. A culture from the left ear yielded a pseudomonas sensitive to coly-mycin and polymyxin and slightly sensitive to neomycin and streptomycin.

A solution containing 1,000 units of bacitracin and 20,000 units (0.6 milligram) of coly-mycin per cubic centimeter with a small amount of local anesthetic added was sprayed into both nostrils with the patient lying on his back, first with the head straight and then with it turned to the left and right sides in order to reach the area of the eustachian tubes. Then 1.5 cubic centimeters of the solution was instilled into the left aural canal and 0.5 cubic centimeter into the right. This permitted some of the solution to run through the ear drum into the middle ear on the left. Both canals were then packed with cotton wet with the solution.

The mother, a nurse, carried out this treatment twice a day at home. When she brought the boy to the office a week later, she reported that the ear was very much better and there was practically no discharge. A culture was taken from the left ear, which yielded no growth. The treatment was continued and a week later further improvement was noted. There was very little drainage and it was seen that the left ear drum was beginning to heal. Cultures were again taken and again showed no growth. When seen at the end of 3 weeks' treatment there was again no growth on culture and no discharge. Ever since that time, over a period of 7 weeks' observation, the ear has given every appearance of being completely free of infection.

This patient represents a very favorable response to locally administered coly-mycin in a chronic otitis media which had been active for many years.

CASE 6. This 56 year old white male was admitted to the hospital with symptoms of indigestion. A roentgenogram had shown a poorly functioning gallbladder with stones and a diverticulum of the fundus of the stomach with a niche indicating an ulcer in the diverticulum. At operation it was elected to perform a cholecystectomy. Some biliary contents were spilled during the removal of the gallbladder. No culture was taken and no local antibiotics were used at operation. The wound was closed with counterdrainage through a lateral incision. No antibiotics were given after operation.

The patient's temperature rose to 101.2 degrees F. on the first postoperative day and to 104 degrees F. on the third day. Administration of full strength combiotic was started. It was given every 8 hours for 2 doses and then every 12 hours. The temperature rose to 104.4 degrees F. on the following day and remained high. After 3 days, administration of the combiotic was stopped and dosage with chloromycetin was started, 1.0 gram twice a day. This also failed to bring the temperature down, so after 5 days aqueous penicillin was started, in a dose of 300,000 units every 3 hours. A culture was taken from the counterdrain site which revealed a hemolytic Staphylococcus aureus resistant to penicillin and tetracycline but susceptible to bacitracin.

There was very little indication that the staphylococcus and the minimal inflammatory reaction around the drain were responsible for the high temperature. It was thought that there must be a deep abscess in or beneath the liver, due to organisms in the spillage from the gallbladder during its removal. These organisms were probably of intestinal origin and the most common bacteria in such cases are Escherichia coli, aerobacter, pseudomonas, or organisms of the enterococcal group. Blood cultures on the fourth, eleventh, twelfth, and fifteenth days failed to reveal the causative organisms.

Declomycin was started on the twelfth postoperative day, 300 milligrams immediately and 150 milligrams every 6 hours, but there was no response. On the fourteenth day one of us (F.L.M.) was called in consultation. Administration of coly-mycin was then started intramuscularly in a dosage of 1 million units (30 milligrams) every 6 hours. The declomycin dosage was continued, although there was little indication for it. The patient's temperature came down to normal, but then rose to 103.2 degrees, so the dosage of the antibiotics was doubled. On the next day the temperature dropped to 97.8 degrees and did not rise above normal thereafter. On the fifth day of treatment the dose of the antibiotics was cut in half and 2 days subsequently they were discontinued altogether. After 2 more days the patient was discharged from the hospital.

Although the causative organism was not determined, it seems reasonable to give credit to the coly-mycin for the control of the infection or possibly to a synergistic action of the two antibiotics which permitted an effectiveness that declomycin alone could not produce.

SUMMARY AND CONCLUSIONS

As a result of these studies it seems safe to conclude that:

1. It has been demonstrated that coly-mycin is an antibiotic which has a strong bacteriostatic or bactericidal action on most of the strains of pseudomonas which have been found in the Jackson Memorial Hospital and in neighboring hospitals in Miami, Florida.

2. Coly-mycin is similar to polymyxin B in this respect. It is also effective against many strains of Escherichia coli, aerobacter, and paracolon bacilli, but not against most strains of proteus.

3. In this series of 20 patients receiving intramuscular injections of coly-mycin, no toxic effects have been observed on the liver, kidneys, or blood-forming organs or on the blood constituents when given in doses of from 1 to 3 million units (30 to 90 milligrams) every 6 to 8 hours.

4. Coly-mycin may be expected to yield a favorable response when used either locally or systemically or both in many different kinds of surgical and genitourinary infections caused by susceptible organisms, particularly by those of the pseudomonas group.

5. Coly-mycin may also be effective when given intramuscularly and locally by aerosol in infections of the respiratory tract as well as locally by mouth in infections of the intestinal tract, when the infections are due to susceptible enteric pathogens.

6. Coly-mycin deserves to find wider employment in infections of this character, when the causative or associated organisms are found to be susceptible on in vitro tests.

7. The importance of taking cultures from any infection before any treatment has been started, obtaining the results of the sensitivity tests as soon as possible, and modifying treatment to meet the requirements of the situation cannot be too strongly stressed. Only in that way can patients get the full value of our knowledge of infections and their behavior after the discriminating use of the antibiotics.

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EDITORIALS

THE PROPHYLACTIC USE OF THE ANTIBIOTICS IN CLEAN SURGERY

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DESPITE ALL ATTEMPTS to make surgical procedures completely aseptic, it is, and probably always will be, impossible. The sources of contamination of a given surgical operation are not apparent in most instances, as is demonstrated by the following report of a patient upon whom I operated before the advent of chemotherapy or the antibiotics. This patient was a healthy male, 55 years of age, who had bilateral inguinal hernias. I performed bilateral inguinal herniorrhaphies on him at the same operation using the same instruments, drapes, gloves, and the operating personnel for both sides. One of the incisions, the second one, healed per primam and in the other, the first one, major wound sepsis developed! There was, and is, no satisfactory explanation of this extraordinary selectivity of infection in this case. Experiences such as this are rare, but they seem to demonstrate that there is an unknown factor in most postoperative wound infections in apparently clean surgical cases. For that reason it seems justifiable to utilize all measures possible, including the prophylactic use of the antibiotics, to prevent postoperative infections in clean surgical cases.

The young surgeons, especially those in training today, have no conception of the problems of sepsis encountered a generation ago. For instance, the relative rarity of serious postoperative wound and pulmonary infections, now, as compared to 25 to 30 years ago, even in the decrepit, debilitated patient, is nothing short of miraculous. Without question, in the main this is the result of the discovery of penicillin by Sir Alexander Fleming and the many other antibiotic agents that have become available since then.

The boundaries of many surgical procedures have been advanced greatly in the past decade and a half. Operations that may require 8 to 10 hours to perform, with many chances of contamination, are carried out with the assurance that the operative site and incisions will heal per primam and that postoperative infections rarely will occur. It is true that this is in part due to the better preoperative and postoperative care and improved anesthesia technique. But even under these circumstances it is very doubtful that the major reconstructive arterial procedures carried out day after day could be performed without some serious postoperative infections in the operative wounds or in the lungs were it not for the prophylactic use of the antibiotics.

Many who read this editorial will disagree with this premise, but few understand what true prophylaxis constitutes. For instance, there are those who believe that the prophylactic use of the antibiotics begins in the immediate postoperative period, let us say, in the recovery room, or within minutes or an hour after completion of an operation. An analysis of the problem clearly indicates

that this is not true because it is during the operative procedure that contamination of the operative wound probably occurs in the vast majority of cases. For that reason antibiotic therapy given in the postoperative period, whether it is administered within a few minutes or an hour later, cannot in the true sense be termed prophylactic since contamination has already occurred and infection has actually begun during the operative procedure.

The actual sources of postoperative infections are obscure in most clean cases. Some of them can possibly be traced to the following, but undoubtedly there are others: (1) cross infection from failure to isolate septic cases even in the modern hospitals of today; (2) carelessness in the cleansing of the hands of the surgical team and the maintenance of their sterility during the operative procedure; (3) failure to accept the nasopharynx of operating room personnel as a source of bacterial contamination; (4) failure to isolate the skin of the patient from the operative wound; and (5) the inability to obtain sterility of the operating room air.

In view of the uncontrollable factors some of which may play a part in postoperative wound infections, even though rarely, it seems justifiable to utilize all measures possible to prevent such complications in the surgical patient, including the prophylactic use of the antibiotics.

The sequence of events resulting in the contamination of a clean wound is not entirely clear, but it seems not unlikely that infection may start in a hematoma that forms postoperatively and becomes contaminated from the bacteria deposited in the surgical wound at the operation, or the organisms possibly may have been blood borne. It is rarely possible to close a large operative field or incision without some "dead space" between different structures and layers of the operative site, so that invariably hematomas of varying sizes develop, and it is believed that it is in these that sepsis frequently originates. Once a hematoma has formed and the blood in it has coagulated in the patient who has not already received antibiotics, it is impossible for these drugs to reach the bacteria in this blood coagulum. Thus the bacteria can multiply and produce a seriously infected wound even with antibiotic therapy that is started after the infection has become apparent.

It would seem logical, therefore, to assume that for the antibiotics to be truly prophylactic they must be circulating in the blood stream during the operative procedure. They will be most effective when administered in this manner, because at the time when contamination occurs during the operative procedure there will be fewer bacteria than at a later date when obvious sepsis has developed. It is important, therefore, that the administration of the antibiotics to be truly prophylactic should commence with an adequate amount given intramuscularly "on call" to the operating room so that there will be an adequate antibacterial level of the antibiotic in the blood and body fluids during the operative procedure. If an operation extends beyond 6 hours, additional antibiotics should be administered to maintain an adequate blood level. In addition, they should be administered at 6 hour intervals for a few days after the operation.

The efficacy of this form of treatment has been demonstrated in the experimental animal by Burke in 1957 in a controlled experiment simulating surgical operating conditions. He was able to demonstrate that, in two groups of animals each infected with a standard number of bacteria, there was far less evidence of sepsis in those which had already received the antibiotics when they were infected than in the animals given them after they had obviously become septic.

One of the chief criticisms of those who do not adhere to the prophylactic use of the antibiotics in clean surgical cases is that the indiscriminate use of these drugs will result in more antibiotic resistant strains of bacteria, so that eventually all our infections will

result from these strains and the antibiotics will no longer control the diseases produced by them. It is my contention, on the other hand, that it is the misuse of the antibiotics by many surgeons and doctors over prolonged periods of time that result in the production of these resistant strains rather than in the prophylactic use of them for short periods. It is still not uncommon to observe their prolonged use in septic cases, in some instances far beyond their period of usefulness, because the surgeon forgets to discontinue them or is afraid the infection will flare up if they are discontinued. From personal experiences of surgical vascular procedures that would have been impracticable 20 years ago because of the danger of sepsis, it has been possible during the past 8 years to perform these operations with an extremely low incidence of infection, less than 0.1 per cent, due it is believed in great measure to the prophylactic use of the antibiotics. Therefore, before laying down rules that these drugs should not be used prophylactically, how much better it would be to rule that when they are ordered, they are automatically discontinued after 3 days unless reordered by the doctor. It is this method that has so successfully controlled the use of the narcotic drugs. Sepsis in an arterial anastomosis suture line can be so catastrophic when it develops that we surgeons in this field of surgery should be permitted to prescribe the drugs that we consider an aid in getting patients well, at least until it has been proved beyond any question of a doubt that this method of antibiotic administration is harmful to others.

It is of utmost importance to point out that whether the antibiotics are used prophylactically or not, the utmost vigilance must be maintained and all aspects of aseptic techniques that were our only prophylactic agents against postoperative infections before the advent of chemotherapy and the antibiotics must be strictly enforced. Not only the surgical operating room team but also others in the operating room and those who take care of patients in the wards must follow the same stringent rules. There are and should be no shortcuts, exceptions, or lapses of technique.

THERAPY FOR GASTRODUODENAL HEMORRHAGE

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Two ASPECTS of the problem of therapy for gastroduodenal hemorrhage merit attention. First is the difficulty of comparing various studies of massive upper gastrointestinal hemorrhage, and second is the decision as to which method of therapy is "best."

The many types of therapy for acutely bleeding gastric or duodenal ulcers attest to the difficulty in their assessment. Each evaluation of the problem tends to concentrate on the results of one particular course of action, either nonoperative or operative. Variations in acuteness and severity of hemorrhage, age and socioeconomic status of patients, background and enthusiasm of personnel, and other variables of place and time make it more difficult to compare accurately the experience of one group with that of another. Published results indicate wide variations in mortality, usually without accurately describing these variables. It is difficult to determine whether or not these mortality differences result from variations in the therapeutic regimen.

As an illustration of the effect of the condition of the patients on the mortality rate for gastroduodenal hemorrhage, our experience has shown that no patient who lost less than 40 per cent of estimated normal circulating red cell mass died of hemorrhage. Similarly, the mortality for those patients over 50 years old was several times greater than for those under the age of 50. It is, therefore, extremely important to know as much as possible about the patients upon whom an evaluation of the problem is based.

Except when no definite program of therapy is used and when operation is employed as a "last resort" in depleted patients, there is no conclusive evidence that mortality rates are reflecting differences in therapeutic regimen. Our experience indicates that there is more than one acceptable way of treating an episode of massive gastroduodenal hemorrhage.

When our group began to study this problem, we adopted the definitions and standards of Stewart and associates. Our hospital is similar to theirs, and it is interesting that the mortality on our service for immediate surgery is now essentially the same as theirs. This is evidence of the usefulness of precise definition of the conditions under which a study is undertaken and indicates that a particular type of therapy will yield comparable results under similar circumstances.

Since results under comparable conditions may be predicted the results of one regimen in one hospital may be compared with a second regimen in another if conditions are similar. Except for the studies of Stewart and ourselves for immediate surgery, these comparisons may only be approximated. However, our study has included nonoperative, selectively operative, and immediately operative regimens carried out in a random fashion so that these three methods may be compared directly. Under similar circumstances, the over-all mortality for these types of therapy has been the same.

Therefore, because reports in the literature cannot be used except to gain impressions of effectiveness of therapy for gastroduodenal hemorrhage and because our direct comparison of immediately operative, selectively operative, and nonoperative regimens has shown no statistically significant difference between them, it is our opinion that no method is conclusively "best." The common denominator which determines the lowest mortality is careful attention to the patients by a team which is acutely interested in the problem, a fact which became clear as the mortality in our

hospital dropped when our study was begun and such concerted effort was made.

Although we believe that no well recognized form of therapy has been shown to be superior to another and have warned against "impressions," we presently favor a regimen in which selected patients are operated upon. Because we have lost relatively young patients from hemorrhage while they were being treated according to the nonoperative regimen and also from pulmonary embolus after early operation, it may follow that operating upon only those patients who continue to bleed severely may reduce these risks to the greatest possible degree. Our experience of no deaths in patients under 50 years old in the group operated upon only if rapid hemorrhage persists supports this thesis. Further, if the operation for the bleeding ulcer is physiologically effective in controlling the ulcer diathesis, the patient also gains prophylaxis against further incapacity.

After comparing different types of therapy for gastroduodenal hemorrhage, we have concluded that no generally accepted method of therapy has been shown to be indisputably superior to another. One may apply successfully any particular regimen if it is well suited to the hospital environment and if it is employed with continual careful attention to the patient. However, early surgical intervention in properly selected cases may yield an irreducible mortality.

WHAT'S NEW IN SURGERY

INTRODUCTION

THE SECOND "What's New" program was presented during the final day's program of the Clinical Congress in October, at San Francisco.

Again, the Surgical Forum Committee requested several individuals to digest the scientific papers presented during the preceding days and to give a summary of what each considered to be new and important in the areas of surgery which they were asked to cover.

These are brief reports and are not intended to include references to all that was considered new and valuable. They are excellent summaries which the Forum Committee and the Editors believe give a view of the progress of surgery. This section of SURGERY, GYNECOLOGY & OBSTETRICS last year was received with enthusiasm by readers and young men in surgical training programs. Reprints will again be made available through the Chiefs of surgical residency training programs for distribution.

The Editors and the Forum Committee appreciate the co-operation and promptness with which the manuscripts were submitted so that they may appear again within 4 months of the conclusion of the program of the Clinical Congress.

ANESTHESIA AND PULMONARY PROBLEMS

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IN PREPARING THIS REVIEW, I have found it difficult to be sure of what is genuinely new. When a report appears which establishes more firmly some previous work then such a report should be considered a part of what is new. Certainly, isolated case reports, series of patients operated upon for bronchiectasis, or cancer of the lung cannot be regarded as new, unless they embody some new concept. In anesthesia, further reports on the use of relatively new agents fall into the same category. I shall endeavor to point out those contributions of the past year in anesthesia and pulmonary problems which seem to me to be significant. Most of these lie in the realm of physiologic concepts.

Let us begin first with the newborn. Asphyxia neonatorum undoubtedly results from a variety of different causes. Westin and associates, proceeding from the observation that a reduction of body temperature in newborn animals is effective in preventing death from experimental asphyxia, made a clinical trial of hypothermia in 6 infants with asphyxia neonatorum. The infants were placed on their backs under running cold tap water (8 to 14 degrees C.) until their body temperatures had fallen to between 23 and 30 degrees C. The time required for this reduction in temperature varied between 4 and 40 minutes. Three of the infants began breathing spontaneously without further treatment, and 3 given oxygenated blood also began to breathe spontaneously. Auditory tests on the infants demonstrated no loss of acuity in contrast to other babies who had recovered from severe asphyxia.

Villavicencio and associates reported on the treatment of the pulmonary hyaline membrane syndrome with the use of human fibrinolysin. This disease has distressed and baffled physicians concerned with the care of the newborn for

many years. The fibrinous nature of the hyaline material lining the functional respiratory surface of the lungs has been demonstrated. Lysis of this hyaline membrane can be accomplished in vitro, using purified human plasmin which has a high fibrinolytic activity. Human fibrinolysin activated with streptokinase was given by aerosol inhalation to a group of 6 babies with the diagnosis of pulmonary hyaline membrane syndrome. Treatment was started 6 to 12 hours after the diagnosis was made. Improvement in the 6 babies took place within 24 hours. All 6 recovered and were discharged with an average hospitalization time of 12 days. Another group of 7 babies with the same diagnosis was treated by conventional methods. Four of these recovered and 3 died. This approach to the treatment of a baffling disease entity certainly merits further investigation and trial.

The cause of hypoxia in patients with left to right shunts and pulmonary hypertension has received some clarification from the report of Ellison and associates. These workers reported experiments on animals and observations on patients. Thirty dogs with systemic pulmonary artery shunts who had developed pulmonary hypertension were studied. After the development of pulmonary hypertension, the arterial oxygen pressure decreased from an average of 89 to 69 millimeters of mercury. The alveolar arterial oxygen pressure differences under the same circumstances increased from 11 to 28 millimeters of mercury. Studies with inhaled oxygen demonstrated that the reduction in arterial oxygen pressure in these animals was the result not only of abnormal diffusion but also of the admixture of venous blood without passage of such blood by reversal of flow through the established left to right shunt. Preoperative and postoperative studies in 13 patients with septal defects or patent ductus arteriosus gave results similar to those in the experimental animal, but of course in the reverse order. Two of the 13 patients, however, failed to show a reduction in the pulmonary hypertension and postoperative studies indicated a markedly lower arterial oxygen pressure than that existing before the left to right shunt was closed. The arterial oxygen pressure decreased even further with exercise with the appearance of obvious cyanosis. The hemoglobin concentration of the blood in these patients rose from 14 to 19 grams. These observations lend additional support to the view that if hypoxia exists in patients with left to right shunts and pulmonary hypertension it is due to the passage of blood through pulmonary arteriovenous anastomoses as well as to abnormal perfusion of the lungs. In the 2 patients who had a lower arterial oxygen pressure after operation, the explanation probably lies in the persistence of flow through the pulmonary arteriovenous anastomoses of blood with a lower oxygen saturation than existed prior to closure of the left to right shunt.

The proper handling of the lungs during cardiopulmonary bypass with an extracorporeal circulation has been a subject of investigation for a number of years. The importance of avoiding an increase in pressure in the pulmonary artery, pulmonary capillaries, and pulmonary veins during the extracorporeal circulation has been well documented. Whether the lungs should be statically inflated, or deflated, or ventilated during extracorporeal circulation under conditions of continued cardiac activity or cardiac arrest has also been studied. Cartwright and associates have made a contribution to this field. They found in experimental animals during cardiopulmonary bypass that when the coronary blood flow was excluded from the pulmonary vessels, by a clamp at the level of the semilunar valves, the pulmonary venous blood most nearly resembled systemic arterial blood when the lungs were statically inflated rather than ventilated or collapsed. Under these conditions the normal collateral bronchial blood flow amounted to only 0.7 per cent of the systemic flow, and the metabolic requirement of the pulmonary tissues was found to be very small, amounting to only 1 or 2 per cent of the total metabolic requirements. On the other hand, when the coronary blood flow was permitted to augment the bronchial collateral flow through the pulmonary vessels, the pulmonary venous blood most nearly resembled the systemic arterial blood when there was mild ventilation of the lungs.

Goetz and associates have reported a number of interesting observations on experimental animals in which the bronchial collateral blood flow had increased 6 to 9 months after ligature of the left main pulmonary artery. They found that the difference in pressure between the right and left atrium determined the direction of venous blood flow from the pulmonary capillaries, either to the azygos system or to the pulmonary veins. They also made the interesting observation that

perfusion of cold blood through the lungs increased the pulmonary resistance, the pulmonary artery pressure, the bronchial collateral blood flow, and the total amount of blood in the lungs. These changes occurred without a rise in the left atrial pressure. These findings may be of some significance in the currently wide application of profound hypothermia with biventricular bypass in human patients.

For some time it has been realized that the pulmonary blood flow through a collapsed lung is decreased. Bjork recently in studies on patients has shown that the blood flow through chronically atelectatic lungs is indeed markedly decreased. Unpublished observations from our laboratory using a square wave electromagnetic blood flow recorder have shown that the pulmonary blood flow through an acutely collapsed canine lung does not decrease during the first hour but decreases gradually during the second and third hours after collapse. The saturation of the systemic arterial blood with oxygen varies inversely with the change in blood flow through the atelectatic lung. At the end of the first hour with the pulmonary blood flow undiminished there is marked unsaturation of the arterial blood with oxygen. During the next 2 or 3 hours, as the blood flow diminishes, the oxygen saturation rises. The significance of these observations are apparent for the surgeon operating in the thorax who must necessarily produce some collapse of the lung in order to work. The surgeon should bear in mind that when his assistant retracts and compresses the lung a right to left shunt is created which reduces the saturation of arterial blood with oxygen. In a patient with cardiac or coronary artery disease this may result in a weakening of cardiac systole and a lowered blood pressure or even cardiac arrythmias or cardiac arrest.

Following the pioneer work of Creech, many investigators in treating cancer have isolated limbs or organs and perfused them with cancericidal agents. Baxter and associates reported studying the tolerance of an isolated lobe of a dog's lung to perfusion with varying amounts of mechlorethamine hydrochloride (nitrogen mustard). They found that the normal pulmonary tissue of dogs will not tolerate perfusions with amounts of nitrogen mustard above 0.2 milligram per kilogram of body weight. With higher doses there was a marked decrease in oxygen uptake, with the development of edema, followed by consolidation, collapse, and fibrosis. There was complete destruction of the normal architecture of the lung in 2 months. It appears probable that different tissues of the body will have different tolerances to concentrations of cancericidal agents. Thus the normal liver has been shown to have a slightly greater tolerance, 0.3 milligram per kilogram of body weight, to nitrogen mustard.

In the field of anesthesia, further clinical and laboratory studies have been conducted on halothane (fluothane). One of the difficulties with this new agent has been the control of its concentration in the anesthetic circuit. This technical problem is well on its way to being solved. There is evidence to suggest that the drug has a depressant action upon the myocardium and that it should be used with caution in patients with cardiac disease. A new agent, carbocaine, has been introduced and is currently being studied.

Probably more important than the discovery and investigation of new anesthetic agents, of which to the surgeon there seems to be a plethora, is the continued study by anesthesiologists and surgeons of methods of pulmonary ventilation in the unconscious patient. Despite the numerous reports that have appeared on this subject in the past 10 years, in certain areas there appears to be no unanimity of opinion. I think it is safe to say that most investigators in this field are agreed: (1) that the spontaneous respiration of the unconscious patient is frequently inadequate to maintain normal concentrations of oxygen and carbon dioxide pressure in the arterial blood, and (2) that regardless of what method is employed of assisting or taking over the patient's pulmonary ventilation a greater volume of ventilation is required under these circumstances to produce the same alveolar ventilation than takes place with spontaneous respiration in the conscious patient. The reason that pulmonary ventilation of the unconscious patient is often inadequate would appear to be due to the inevitable depressant action of the anesthetic agent upon the normal mechanisms of respiration. The reason why a greater minute volume of ventilation is required when ventilation is assisted or controlled almost certainly lies in altered ventilation-perfusion ratios in the lung. The substitution of a positive pressure in the trachea during the inspiratory or inflation phase for the slightly negative intratracheal

pressure during normal inspiration must set up air currents which result in the passage of too much gas to certain portions of the lungs and insufficient amounts to other portions. A study of the distribution of gases within the tracheobronchial tree during inflation under these two circumstances would be of interest.

A number of articles on methods of ventilation under anesthesia have been reviewed by Saklad. There still appears to be little agreement among anesthesiologists concerning the advantages or disadvantages of devices which are volume regulated, as opposed to pressure regulated. This disagreement persists despite the well known, well documented fact that the employment of high intermittent positive pressure ventilation will result in a fall of cardiac output in patients with a closed thorax. It is practically impossible to predict the required minute volume ventilation which will result in normal oxygen and carbon dioxide pressures of arterial blood in unconscious patients of various ages, weights, sizes, positions on the operating table, and varying degrees of impaired pulmonary or cardiac function. Because of the factor of position, or impaired cardiac or pulmonary function, it is impossible to determine the required minute volume by estimating surface area. When using oxygen enriched anesthetic gas mixtures, the only clue to adequate alveolar ventilation lies in the determination of the carbon dioxide pressure of arterial blood. Currently there is no practical method of continuously determining this in the anesthetized patient. The nearest estimate can be obtained by continuous sampling of the patient's end-expired gas and passing it through an infrared carbon dioxide analyzer. The physiologic dead space increases when assisting or controlling respiration. The greater this physiologic dead space, the greater will be the discrepancy between the oxygen pressure of the end-expired gas and the carbon dioxide pressure of arterial blood. Normally the physiologic dead space (defined as that portion of total ventilation which is not alveolar ventilation) is not higher than 30 or 35 per cent. When ventilation is assisted or controlled the physiologic dead space usually rises to 55 or 60 per cent of the total ventilation. Under these circumstances the carbon dioxide pressures of arterial blood is less than 5 millimeters of mercury, higher than the carbon dioxide pressure of the end-expired gas. When the physiologic dead space rises as high as 80 per cent of the total ventilation, the carbon dioxide pressure of the arterial blood may be as much as 15 millimeters of mercury higher than the carbon dioxide pressure of the expired gas. Despite this discrepancy, monitoring the adequacy of pulmonary ventilation by determining the carbon dioxide pressure of expired gas is the only practical method available at present.

In our opinion, the best method of producing an adequate alveolar ventilation without reducing cardiac output is to employ a positive and negative pressure ventilator monitoring the end-expired gas and varying the positive and negative pressure so as to produce a tidal volume, at a normal or near normal respiratory rate, which will maintain the carbon dioxide pressure of the end-expired gas in a normal range. To use an intermittent positive pressure device which is set to deliver a certain tidal volume regardless of the positive pressure required to produce this tidal volume would appear to be both absurd and dangerous to the patient.

Although any marked degree of hyperventilation is difficult if not impossible to achieve in anesthetized patients with the currently available methods of ventilation, nevertheless, the physiologic effects of hyperventilation quite properly are being studied. Sugioka and Davis determined the oxygen tension of the cerebral cortex in dogs hyperventilated with pure oxygen. Hyperventilating with pure oxygen produced a fall in cerebral cortical oxygen tension, while breathing mixtures of 10 per cent carbon dioxide and 90 per cent oxygen produced an increase in the oxygen tension. These effects were undoubtedly related to the carbon dioxide pressure of arterial blood which, when it is high, produces vasodilatation of the cerebral vessels and, when it is low, vasoconstriction. These experimental observations should be confirmed and amplified. The carbon dioxide pressure of arterial blood was apparently not determined in these experiments. The experiments were acute and consequently it was impossible to determine whether the drop in cerebral cortical oxygen tension was deleterious, because it was not possible to study the physiologic and pathologic effects in surviving animals. Earlier studies by Rand and his associates and by others would indicate that degrees of hyperventilation which can be achieved by current methods in the anesthetized patient are without either temporary or permanent damage to the brain.

Prolonged artificial ventilation of postoperative patients for weeks with ultimate recovery have been reported by Bjork and others, and most recently by Bahnson. Such artificial respiration through a tracheostomy should be employed without hesitation in many patients with inadequate respiration postoperatively and will often be lifesaving. When major intrathoracic operations are performed, placing a small plastic catheter through a stab wound in the pulmonary artery and allowing it to remain in place during the postoperative period for a number of days permit the easy sampling of mixed venous blood, which gives an excellent indication of the adequacy of the cardiorespiratory function in the postoperative patient.

CARDIOVASCULAR SURGERY

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INTEREST in the problems of the cardiovascular system has continued to occupy a prominent position in surgical thinking as demonstrated by the persistently productive efforts of many of our more senior colleagues and by an overwhelming amount of work produced in recent months by the younger men. To do justice to this prodigious volume of material is an impossible task and this is a summary of some of the highlights.

Hypothermia, considered by some surgeons to be an unfashionable adjuvant in the cardiac field, continues to be used actively by others and is being more extensively employed in combination with extracorporeal circulation.

Using a combination of extracorporeal circulation and hypothermia, Kameya, Oz, Neville, and Clowes have studied the influence of various flow rates on oxygen consumption at moderate and profound levels of hypothermia. Their studies indicated that during profound hypothermia an oxygen debt with its metabolic consequences can occur with low flow perfusions despite the great reduction in the rate of oxygen consumption.

Continuing their studies of extracorporeal circulation and hypothermia, Lesage, Freeze, Young, and Sealy reported an excellent survival rate in a group of animals cooled to less than 7 degrees C. by means of a heat exchanger incorporated in a pump-oxygenator system. Complete circulatory arrest without perfusion was maintained for periods up to 60 minutes, followed by rapid rewarming. Relatively few serious sequelae resulted in surviving animals, although cerebral damage was sustained by several dogs.

Gordon, Myer, and Jones have also studied both experimentally and clinically the use of deep hypothermia for cardiac surgery without the use of an oxygenator. Both animals and patients have been cooled by an extracorporeal technique to temperature levels below 10 degrees C. with periods of total circulatory arrest up to 60 minutes. A variety of intracardiac procedures has been conducted with very good success. None of the patients in the clinical series showed any evidence of damage to the central nervous system. Drops in *p*H and carbon dioxide during and after rewarming, attributed to a moderate rise in lactic acid, were observed but in the clinical cases no treatment was required for postoperative acidosis.

A number of contributions were made to diagnostic angiography.

Lance and Killen reported that the use of 20 per cent glucose injected into the aorta immediately prior to an injection of 70 per cent urokon protects against renal injury. They used a standard test dose of urokon sufficient to produce azotemia in 100 per cent of control animals; after glucose infusion azotemia developed in only 22 per cent of animals with the standard urokon injection. Survival of animals was also enhanced by preliminary glucose administration.

Bernstein and Evans have demonstrated that infusions of low molecular dextran afford protection against the toxic effects of large doses of 90 per cent hypaque. The mechanism of the protective action remains obscure but since low molecular dextran has been shown to prevent intravascular sludging seen during prolonged cardiopulmonary bypass and after trauma it is

suggested that the protective action is related to the stability of the red blood cell suspension.

Stephenson, Figley, and Phillips have explored the possibilities of venous inflow occlusion during angiocardiography as a means of increasing the definition of structures with smaller doses of contrast materials and of improvement of techniques for coronary arteriography. They used a balloon-tipped catheter inflated in the vena cava or right atrium for transitory inflow occlusion. The normal dog apparently tolerates such occlusion well for 1 or 2 minutes at the time with reversible electrocardiographic alterations occurring at about 30 seconds; excellent coronary arteriograms were obtained.

Longenecker, Reemtsma, and Creech have studied the development and regression of collateral circulation associated with acute occlusion of the superficial femoral artery and its release by methods involving serial arteriograms, cine fluorography, and distal pressure tracings. Their studies suggest that the pressure gradient across the site of occlusion results in the opening of pre-existing collateral channels very promptly. These collateral channels regress with equal promptness when the gradient is removed by restoration of blood flow.

Leland Clark has reported a new method for continuously measuring and recording oxygen content of blood, which requires only 0.3 cubic centimeter of blood per minute. Hemolyzing ferricyanide solution and blood are pumped at a ratio of 20 to 1 with a proportioning pump and mixed in an anaerobic microcuvette with a magnetic stirrer, and the oxygen tension of the resulting fluid is measured with a Clark oxygen electrode. The recording lags 90 seconds behind the actual blood content, and results agree with Van Slyke analysis to within 2 per cent.

Pfaff, Frommer, and Morrow have employed the polarographic techniques described by Clark for recording indicator dilution curves from an intravascular site in the course of cardiac catheterization using ascorbic acid as the indicator. The sensing device is a platinum electrode which is introduced into a peripheral artery or positioned in a cardiac chamber through a catheter or transeptal needle. Ascorbic acid in the immediate environment of the sensing electrode produces an increase in electric current that is proportional to the concentration of this reducing substance. The signal is amplified and recorded as a continuous dilution curve. Correlation with dye dilution curves has been excellent. The advantages of the ascorbic acid technique seem to be that blood sampling is unnecessary, the distortions of sampling techniques are obviated, and a physiologic substance is employed as the indicator.

Blaisdell and Cooley have studied the incidence of paraplegia in dogs following descending thoracic aortic occlusion to determine if this could be altered by increasing or decreasing the spinal fluid pressure. They found that spinal fluid pressure increased after thoracic aortic occlusion to an average of 15 millimeters of mercury, equalling that in the aorta distal to the occluding clamp. With the period of occlusion used the incidence of paraplegia was 50 per cent. However, if spinal fluid pressure was kept equal or slightly above distal aortic pressure the incidence of paraplegia was 100 per cent in a similar test period. Conversely, if during aortic occlusion the spinal fluid pressure was lowered below 5 millimeters of mercury by withdrawing fluid or by the intravenous use of urea, the incidence of paraplegia fell to 8 per cent. They concluded that reduction in spinal fluid pressure provides a sufficient pressure gradient between aortic tributary and spinal vessels to provide a minimal arterial flow into the cord substance in spite of low pressure which exists in the abdominal aorta.

Gerein, Jones, and Cross have made a critical study of the possibilities of providing circulatory support to the failing heart by cardiac bypass with a pump-oxygenator. Using Sarnoff's tension time index as a means of assessing the oxygen requirement of the heart they carried out studies in normal dogs employing (1) partial circulatory support, (2) complete circulatory support, and (3) complete circulatory support with no blood returning to the left ventricle. Their results indicated that the tension time index is not substantially decreased during partial and complete circulatory support. There was a significant decrease in tension time index during complete circulatory support when blood is excluded from the left ventricle. They concluded that circulatory support is of no significant value in decreasing oxygen consumption of the heart by removal of a volume of venous blood returning to the heart. If circulatory support increases the aortic pressure, the tension time index is increased, and this in turn may be detrimental to the shocked or failing heart.

Rutherford and Swan have also been interested in prolonged partial perfusions as a means of reducing the heart's work. They initially assessed the effects of prolonged venoarterial shunting without oxygenation. The most significant problem which developed was hypoxic acidosis. By counteracting this with a continuous infusion of sodium bicarbonate it was possible to achieve survival in a group of animals perfused for 12 hours without oxygenation. In a similar series of oxygenated perfusions it was possible to use much less sodium bicarbonate to offset acidosis and survival rates were good in 12 hour perfusions although the animals did not tolerate the procedure as well as those perfused without oxygenation.

Krasna, Steinfeld, Kreel, and Baronofsky have used prolonged venovenous pumping with oxygenation in an effort to determine whether such perfusion could be of assistance to an individual with severe decrease in pulmonary function during periods of stress. Their technique was to drain blood from a femoral vein into an oxygenator and return it into a jugular vein. Perfusions were continued up to 10 hours. These perfusions were well tolerated although plasma hemoglobin rose to very high levels in some instances. In animals rendered cyanotic by breathing a low oxygen mixture venovenous pumping with oxygenation at a rate of 600 cubic centimeters per minute was capable of elevating the arterial oxygen saturation of a cyanotic animal by 20 to 40 per cent.

Borden, Fonkalsrud, Newcomer, Longmire, and Rochlin have applied the techniques of isolation perfusion in the treatment of snake bite using antivenin in the perfusate. After injection of 3 minimum lethal doses of pooled rattlesnake venom into the leg of dogs a tourniquet was applied, and after varying periods of time femoral vein and artery were cannulated. Antivenin was injected distally into the arterial cannula while equal aliquots of blood were concomitantly removed through the venous cannula. The perfusion technique greatly improved the mortality and morbidity statistics in the experimental group as compared to control animals. This method appears to be a practical contribution but it has not yet been applied clinically.

Foote, Trede, and Maloney have made a careful study of the possibility of using ordinary stored and banked blood instead of freshly drawn heparinized blood in the operation of a pump-oxygenator program. Their study has demonstrated that the myocardial toxicity of citrated blood is not inherently due to citrate but to "calcium binding." Preliminary studies in dogs assessing electrocardiographic changes and direct measurement of myocardial contractility during coronary perfusion made it possible to determine the amount of calcium necessary to nullify adverse myocardial effects of citrated blood. Clinical application of these data resulted in comparison of the physiologic effects of heparinized and "converted" A.C.D. blood in a series of 18 patients undergoing extracorporeal circulation. Results have shown this to be a practical and safe plan.

Two new pump-oxygenators were described. One, devised by Roe, Weirich, Moore, and Swenson, is a semidisposable screen oxygenator. The other, developed by Barsamian, Jacob, and Collins, has a pump powered by an oxygen tank and a set of rotating steel cylinders in the oxygenator. It is small, compact, completely autoclavable, and efficient and has a priming volume of 1 liter. Barsamian believes a commercially developed model can be made to sell for about a thousand dollars.

Among several interesting reports on atherosclerosis was that of Sako who has studied the effect of hypertension on experimental atherosclerosis. Thoracic aortic coarctation was first produced in a series of dogs. In test animals hypercholesterolemia was induced by an atherogenic feeding regimen while controls remained on stock diet. Studies carried out over a 6 month to 3 year period in these animals indicated that the atheromas appear first and with much greater severity in the hypertensive part of the circulation of animals with coarctation, and the greater the differential in pressure the more striking the effect was. It also appeared that atheromas appeared in areas of hypertension at a lower blood cholesterol level than that which produces comparable lesions in controls. These observations lend support to the clinical concept that hypertension is one of the contributing factors in atherogenesis.

Jude, Kouwenhoven, and Knickerbocker have developed a new method of resuscitation in cardiac arrest without using open thoracotomy. The method involves the use of heavy pressure on the lower sternum to compress the heart between sternum and thoracic vertebrae in rhythmic fashion 60 to 80 times per minute. Experi-

mental studies in dogs have shown that mean and pulsatile femoral arterial pressure and carotid flow are maintained at 40 to 60 per cent of control values by this method with the heart in ventricular fibrillation. Permanent survival without evidence of cerebral damage occurred in 10 animals maintained in ventricular fibrillation for periods up to 30 minutes while circulation was maintained with external cardiac pressure. Extensive application of the method to clinical cases has been made. Resuscitation was 100 per cent successful in the operating room type of cardiac arrest due to hypoxia, vagovagal stimulation, or anesthesia. While resuscitation of a great variety of cardiac arrests in a miscellaneous group of medical and surgical patients on the wards and in the emergency room was complete in 61 per cent, over-all resuscitation by the method was successful in 41 of 57 cardiac arrests due to all causes in all locations.

Smith and McEachen described the long range results of the Dammon-Muller procedure of constricting the pulmonary artery in infants with large left to right shunts. In 7 of the original group of patients on whom this procedure was done close follow-up with clinical and catheterization data over a 6 to 8 year period has indicated an excellent postoperative physiologic response. Several of these patients have undergone subsequent successful reconstruction of the pulmonary artery with closure of the ventricular septal defect.

Lower and Shumway have developed a technique for homotransplantation of the canine heart which demonstrates that it is feasible to remove the dog's heart and replace it with an homologous heart with survival of recipient animals for several days. The donor heart is refrigerated initially to 4 degrees C. and circulation of the recipient animal is maintained by pump-oxygenator during transplantation. The technique involves leaving intact the posterior atrial wall containing the ostia of both venae cavae and the pulmonary veins. The homologous heart is then joined to the edges of the posterior atrial wall, a ridge of the atrial septum, the pulmonary artery, and aorta. The results in survivors demonstrate that the denervated homologous heart functions apparently normally until the immunologic rejection mechanisms of the host produce a lethal myocarditis.

Hering, Hovnanian, Olwine, Brennan, and Watkins have been interested in the possibilities of applying a high frequency sound probe to calcium deposits in a diseased cardiac valve, as a means of removing such deposits during open cardiac surgery. However, they first studied the effects of ultrasound on normal valvular and endocardial tissue and the conduction system. An ultrasound probe with a primary frequency of 26,000 cycles per second was applied in dogs to the tricuspid valve leaflet and the area of the atrioventricular conduction bundle for periods of 60 seconds. Animals were sacrificed at periods up to 8 months after operation and microscopic study of the tissues revealed that an intense inflammatory response is induced in normal leaflet substance by 1 minute applications of ultrasound. The reaction closely simulates rheumatic valvulitis. No evidence of conduction disturbances resulted from application of the ultrasound probe to the area of the atrioventricular node or bundle.

Experimental mitral valve replacement by using a variety of prosthetic valves was described by Howard, Willman, and Hanlon as well as by Starr. The problems of fixation of the valve to the mitral annulus and of thrombosis were prominent in both studies. A lucite caged silicone rubber ball valve fixed by knitted teflon cloth to the annulus has evolved from Starr's study and looks encouraging.

Reports concerning vascular surgery were concentrated on the problems of anastomosis of very small arteries.

Carton, Kessler, Seidenberg, and Hurwitt described a nonsuture technique of anastomosis of small arteries and veins using a flanged ring prosthesis. The end of the vessel is brought through the prosthesis and everted with plastic adhesive (methyl 2-cyanoacrylate) between vessel and prosthesis. The everted vascular cuff is covered with adhesive, and flange and vessel are invaginated into the distal vessel. Reinforcement of the anastomosis is achieved with adhesive plus vein or fascia. Early good results in a series of arterial and venous anastomosis in dogs were reported.

Holt and Lewis described a nonsuture technique for small vessel anastomosis employing vascular cuffing over 2 small teflon rings, each of which contains tiny pin holes. Alternating pins are used to secure the vascular cuff to the ring. The 2 rings are then aligned and pressed together so that the pins of one enter the alternate unoccupied holes of the other and the intima of

opposing vessels is brought into contact. Early results are encouraging.

Ratan, Leon, Lovette, Levowitz, Magovern, and Kent have developed a direct nonsuture technique of anastomosis of the internal mammary artery to the left coronary. This procedure involves cuffing the distal end of the divided internal mammary over a specially constructed nylon stent and inserting the stent into the distal segment of coronary artery with fixation by a single ligature. In about one-half the dogs a patent anastomosis was obtained as demonstrated by electrocardiography and by angiocardiography for periods of as long as 6 to 12 months.

Rohman, Goetz, and Dee have anastomosed both left and right internal mammary arteries to the left anterior descending and circumflex coronary arteries in such a way that except for the septal branch the entire left ventricular blood supply originates from the mammaries. The cut end of the internal mammary is evaginated over a tantalum ring and the cuffed vessel is then inserted into the coronary beyond a ligature. Anastomotic patency for periods as long as 18 months was described and the incidence of thrombosis was approximately 15 per cent.

An interesting method has been devised by Jacobson and Suarez for carrying out microsurgical anastomosis in very small arteries by using a dissecting microscope, miniature surgical instruments, and a swinging arm device for the control of vascular clamps. Multiple very small stitches of Nos. 7-0 and 8-0 silk and nylon are used and the extremely meticulous anastomotic technique has resulted in an excellent patency record.

Deaton, Anlyan, and Fort have developed a standard preparation for the production of intra-arterial thrombosis by mechanical intimectomy. In a large series of animals various treatment regimens were employed, including (1) heparin, (2) streptokinase-plasminogen, (3) heparin following streptokinase-plasminogen, and (4) plasmin. Their results indicated that plasmin was the most effective agent in the prevention and treatment of thrombosis of small arteries. Application of the plasmin regimen to a group of clinical patients has been initiated and results are encouraging.

FLUIDS AND METABOLISM

SHOCK

BURNS, WOUND HEALING, AND INFECTION

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THE PAPERS which pertain to the three categories of fluids and metabolism, burns, wound healing, and infection, and shock were excellent.

The paper by Bradshaw and Abbott involved a practical study of insensible water losses in patients undergoing laparotomy. The essential feature of their presentation is that this water loss was far greater than one might anticipate. In preoperative control patients at bed rest it was 1,000 milliliters per 24 hours. In an uncomplicated case it would be 500 milliliters; but in a complicated case, possibly 2,000 or 2,500 milliliters. These figures are equivalent to one-sixth to one-third of the plasma volume. Animal experiments indicated that the immediate rise postoperatively is especially associated with operations which involve extensive exposure of moist tissues, such as when the intestines are out of the abdomen. Therefore, the clinical implication is that one should pay more attention to restoring this water loss.

Berkas and Grim made a comparative study of the absorption of sodium, chloride, and water from isolated loops of jejunum, ileum, and colon, down the intestinal tract in that order. The reason for this study was to relate this absorption to the hyperchloremic acidosis that follows some of the urinary diversion procedures. The essential finding was that the absorption was progressively greater aborally in the in-

testinal tract. Thus, the chloride absorption rate from the jejunum was about half that from the ileum, and one-seventh that from the colon. Furthermore, relatively far more chloride than sodium was absorbed from all but the jejunum, where an equivalent ionic ratio was maintained. These investigators concluded, therefore, that their studies support the use of jejunum for urinary diversion as a means of minimizing hyperchloremic acidosis.

Zimmerman, Pressman, Cohn, Carr, and Schloerb made studies on dogs indicating that the spleen and small bowel are important sites of uric acid production. In human beings, admittedly with a somewhat different uric acid metabolism than dogs (except for the Dalmatian hound, I might add), it is conceivable that in intractable cases of gout splenectomy plus possible small bowel resection might be adopted as a mode of therapy.

Bell, Hume, and Egdahl presented an important aspect of research technique indicating that studies of adrenal cortical secretion involving experiments in which bacterially contaminated blood is used may be fallacious. Such blood alone serves as a maximum stimulus to corticosteroid output from the adrenals, whereas sterile blood is not at all a stimulus.

Cahill, Kinney, Nichols, and Brann reported experiments indicating that maintenance of caloric equilibrium during the immediate postoperative period did not eliminate the increased nitrogen excretion usually characteristic of this period.

Coon postulated that ascorbic acid requirements in surgical patients may not be as high as previously considered; however, many of his patients were old.

Garrett, Jordan, and Hettig showed that there is a marked increase in serum gamma globulin after thymectomy in dogs.

Two papers on somewhat the same subject by Gabel, Cox, Zabor, and Economou and by Fitts and Neely reported 2 new experimental preparations to study bile pigment and bile acid metabolism in dogs. These were respectively a special biliary-renal and a special biliary-caval anastomosis.

Breed and Dumont discussed renal lymph formation rate and showed that it is not entirely parallel to urine formation rate.

Richardson and Watkins made blood volume studies in pediatric surgical patients. Their findings are, in my opinion, of great significance for those who operate on infants and children. The striking feature was the frequency in anemic patients of a low red cell mass, but with a high plasma volume. The resulting total blood volume tended to be above normal even in the tumor patients. Two inferences can be drawn from this study: first, that there should be a greater use of packed red cells, in contradistinction to whole blood, in some of these patients; and second, that the chronic shock hypothesis, at least as so interpreted by many physicians, should be adopted with even more caution than in the past.

Williams, Williams, Stoddart, Hindel, and Fine presented an interesting mechanized method for determining blood volume in patients—the volémetron which appears to have possibilities and may prove to be a valuable adjunct to the care of the surgical patient.

King and Price and Conn, Fain, and Ferrington presented two methods to differentiate full thickness from nonfull thickness burns. The first of these groups of workers used an intravenous method: Evans blue dye in humans in a dosage of 1.4 milligrams per kilogram was injected intravenously; and, in this method, the third degree burns were not stained, whereas there was a color-ring around them, differentiating very sharply where the total destruction was. The second group of workers used local direct injections of sky blue, 0.4 per cent, 0.5 milliliter. If there was total destruction, there was no lymphatic spread. If there was not total destruction, there was lymphatic spread. This is certainly a very fundamental problem and one that should be elucidated further.

Strain, Pories, and Hinshaw studied zinc metabolism in skin repair. Zinc hastened wound and burn healing in rats, especially with sulfuramino chelates. These investigators showed that in postoperative patients—for example, after gastrectomy—the hair and skin zinc content falls very markedly, and they even postulated the advisability of parenteral zinc treatment in surgical patients submitted to severe trauma.

Alexander, McGloin, and Altemeier carried out experiments using a very ingenious buried string technique to study penicillin prophylaxis in experimental Staphylococcus auereus wound infections. Certainly these studies provide a tool for future similar studies, but they indicated that aqueous penicillin-G intramuscularly is pro-

tective in these guinea pigs. In answer to a direct question they do not use prophylactic penicillin routinely in treating their patients.

Shelby, Cotlar, Massari, Atik, and Cohn studied antibiotics in experimental bile peritonitis. Their work confirms the belief that fluid loss, while important, is not the only factor, because a single intramuscular injection of penicillin, even if given 8 hours after onset, caused survival of the animal. All untreated dogs died.

Levenson, Malm, Horowitz, Moncrief, and Trexler's paper is of great fundamental interest and may well represent something we will be doing before too long. This presentation concerned a disposable plastic isolator for operating in a sterile environment. The surgeon and assistants place their hands and arms into the bag through a helmet-jacket arrangement with long gloves and sleeves. Instruments can be passed by lock, as in a submarine, or by a separate bag attached by heat-sealing and then cut. Sponges can go in an attached sleeve so that the nurses can count them. There is positive air inflow, cleaned by an adequate filter proved by years of use in the germ-free experiments, into the bag. Hence, in emergencies instruments can be passed in and because of the high air pressure the current will only be going out, and there will not be contamination. Other uses of such a bag might be (1) to isolate susceptible patients—for example, those with low white counts or radiation injury—and place them in the bag where they would be completely separate from all outside contamination; (2) to isolate patients with dangerous infections during the time they have such infections, so as to protect others in the same ward; (3) to isolate burns in an environment which also does not introduce any extraneous bacteria but is also one in which humidity control is simple; (4) furthermore, surgical infections can be studied now with a new tool, and the relative role of operating room contamination and other factors can be studied because the operating room contamination from outside can be completely eliminated by this method.

Cowley, Demetriades, Mansberger, Attar, Esmond, and Bessman studied extracorporeal circulation and, under certain circumstances, found that it was favorable in shock in dogs. In irreversible shock, the liver may not be able to keep up in supplying glucose with the tissue needs for this carbohydrate.

Strawitz and Hift studied glucose metabolism in shock. One of the most important points brought out was that they found a uniform hyperglycemic peak in all cases just before the collapse of the blood pressure.

There were two important papers concerning norepinephrine in its relationship to urine flow in hemorrhagic shock—by Wulsin and Altemeier and by Jackson and Webb. These investigators were in essential agreement and found that urine flow depends more on blood volume-deficit replacement than on blood pressure. If urine flow is better with replacement, then, under that circumstance, norepinephrine actually suppresses urine flow, although there is a secondary diuresis. Blood reinfusion would seem to be far superior to vasopressors.

Cooper, Rosenthal, Foroff, and Blakemore studied the action of norepinephrine and ascorbate on progesterone hydroxylation. This is a fundamental study and essentially showed that the catecholamines help this particular reaction, but that ascorbate hinders it.

Grage, Winter, and Zimmermann studied the regulation of antidiuretic hormone. Moderate hemorrhage produces an antidiuresis in dogs. This does not appear to be due to a decrease in renal blood flow. These investigators believe, therefore, that it is due to a release of antidiuretic hormone. This release is unaltered by bilateral cervical vagotomy. From the differential standpoint, free water clearance is the one modality which is markedly reduced, as evidenced by the rise in urine osmolarity paralleling the fall in urine volume flow.

Myers, O'Hara, Heizer, Liberman, and Marks studied the corticosteroid response to surgery. This study is of practical value in all types of extensive surgery. The uniform corticoid response to surgery, concerning which we have heard so much in the last few years, can be counteracted by increasing the circulating or exogenous corticoids. For example, if one administers dexamethasone phosphate—4 milligrams per hour beginning an hour before operation and continuing through operation, e.g., a gastric resection—this will entirely prevent the usual corticoid response to an abdominal operation. Thus, the response depends on both the stimulus and the need as reflected by the circulating blood level of 17-hydroxycorticoids. The only point which must be decided is whether this response is good or bad, and do we want to pre-

vent it? But at least we know now how it can be prevented.

Paloyan, Harper, and Watkins reported on the endocrine control of plasma lipids, based on the hypothesis that the hyperlipemia in dogs which follows subtotal pancreatectomy might be a manifestation of glucagon deficiency. They used the observation that one part of the pancreas (uncinate process) contains only alpha cells, while the tail contains only beta cells. They concluded that "hyperlipemia with associated hypercholesterolemia is a manifestation of glucagon deficiency, and this substance originates solely in the alpha cells of the pancreas." This observation may well be of clinical importance. One might postulate that before long those with atherosclerosis in its incipient stages might be taking glucagon; but again, this will not occur tomorrow.

I should like to postulate that since elastase, which acts upon the elastin of arterial walls, also comes from the pancreas, it may well be that a deficiency (or excess) of elastase may act upon traumatized arterial walls so that hyperlipemia, supposedly caused by the glucagon of pancreatic origin, will then act upon those affected vessels.

GASTROINTESTINAL BILIARY CONDITIONS

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INGENIOUS and searching studies on almost every region of the alimentary tract, pancreas, and biliary system have been made. For the most part, reports on the studies represent preliminary or early results of studies concerned with new ideas or new approaches to old problems. Some of the ideas and statements herein presented will undoubtedly be subject to considerable revision as additional experimental results and experiences are accumulated and analyzed.

The increasing incidence of alimentary tract ulceration and perforation, particularly in the gastric and duodenal area during prolonged cortisone administration, has been noted for a number of years. Butterfield, Roverud, Bassett, and Cooper have attempted to shed light on the question as to whether cortisone acts to produce such ulcerations by increasing gastric acid-pepsin secretion or by altering the tissues of the gastrointestinal tract.

Perfusion of the esophagi of normal cats with the gastric secretion of cats treated with cortisone produced mucosal edema, whereas when the esophagi of cats treated with cortisone were perfused with the gastric secretion from normal or untreated cats, ulceration and perforation were noted. They concluded that cortisone produces peptic esophagitis in the perfused cat's esophagus by its action upon the tissues rather than by gastric acid-pepsin secretion increase.

The studies of three groups were concerned with the action of the esophagogastric or pyloric sphincter. Carveth, Schlegel, Code, and Ellis found that in dogs subjected to a bilateral subhilar vagotomy, resting pressures in the cardiac sphincter were decreased. However, the occurrence of a response, particularly the occurrence of relaxation, was seriously reduced, and this, apparently, was the cause of the dysphagia and regurgitation of food which usually followed vagotomy in the dog.

In an attempt to provide a means of preventing reflex esophagitis, Ingram and Muller wrapped an innervated flap of diaphragmatic muscle about the mucosa of the lower end of the esophagus, interposing the flap between the esophageal and gastric musculature. They reported a contraction of the flap with each respiratory cycle and a decreased incidence of esophagitis in dogs with a functioning diaphragmatic flap following lower esophageal resection and gastroesophagostomy.

Symbas, Killen, and Scott replaced the resected gastric pyloric sphincter with an isoperistaltic, 4 to 5 centimeter segment of ileocecum which contained the ileocecal sphincter. Gastric emptying was normal or slightly prolonged in each animal so treated. There was a rapid transit of the barium meal from the small to the large intestine in these animals, but they all remained healthy and gained weight during the 11 to 23 month postoperative period.

Our knowledge of gastric physiology and the relation of various factors to the production of peptic ulcer continues to be a fertile field for the surgical investigator.

Seirafi, Jansons, Ruiz, and Reid have stimulated a current periodic reawakening of interest in the importance of local factors in the etiology of peptic ulcer, a concept originally attributed to Virchow. By the injection of polyethylene microspheres into the dog's left gastric artery, typical peptic ulcers were regularly produced on the lesser gastric curvature.

From this somewhat unphysiologic preparation, it is suggested that peptic ulcer develops essentially because of a vascular disturbance. Obviously, such a proposal will require much further study to supplant the evidence of Dragstedt and his co-workers, as well as others, who have so firmly established the prime importance of acid-pepsin digestion as the important factor in the production of peptic ulceration, at least in the duodenum.

In 1942, Dragstedt reported that duodenal ulcer developed in 100 per cent of dogs with external total pancreatic fistula, whereas dogs in whom the pancreatic ducts had been ligated had only a 29 per cent incidence of duodenal ulcer. A marked increase in gastric secretory output was noted to accompany the establishment of an external pancreatic fistula. Greenlee, Johnson, Nelson, and Dragstedt have extended these observations to show that a significant increase in gastric secretion follows pancreatic duct ligation.

Elliott, Passaro, and Elliott were able to reduce the incidence of peptic ulceration markedly in dogs with total external pancreatic fistulas by maintaining adequate hydration and electrolyte balance. Such measures, they believed, aided the mucosa in maintaining resistance to acid-pepsin erosion. The relationship of pancreatic function to gastric secretion is still not completely settled, but at least these latter findings tend to discount the presence of additional unidentified hormones or other factors as relating the pancreas to gastric secretion.

Johnson, Dragstedt, Singer, and Oberhelman have conducted further studies to elucidate the relationship of antral and fundic denervation to gastric secretion. Their studies indicate that (1) the denervated antrum tends to be less responsive to stimuli than when innervated, (2) antral denervation in itself does not produce gastric stasis, and (3) the increased gastric secretion from a Heidenhain pouch after vagotomy of the main portion of the stomach is not the result of antral denervation but of factors resulting from fundic denervation. These investigators also presented evidence to indicate that vagotomy enhances the "intestinal phase" of gastric secretion which results from a loss of acid inhibition rather than increased stasis of intestinal contents in the duodenum.

The role of "acid inhibition" mechanisms of the antrum and duodenum in the regulation of gastric secretion were studied by Shrock, Shapira, and State. Their findings would suggest that antral "acid inhibition" is partly responsible for the decline in gastric secretory rate that occurs during the gastric phase of the prandial response, but the role of duodenal inhibition is insignificant.

The puzzling observation that the plasma volume reduction that follows the introduction of osmotically active solutions into the jejunum is associated in some postgastrectomy patients with "dumping" symptoms, whereas in the majority of them it produces no symptoms whatsoever, has been subjected to further study by Hickler, Brooks, Hamlin, and Hoskins. Their preliminary data on a small group of patients suggest that patients with the "dumping syndrome" have an abnormal response to the circulatory stress of acute postural change. This was indicated by a failure to mobilize adequately the sympathetic nervous system, and in some cases by a concomitant parasympathetic overactivity.

Further support of the theoretic advantage of the Billroth I anastomosis over gastrojejunostomy has been presented by Main, Scott, and Gobbel, who studied the alterations of fat digestion following these two procedures in man. Their gastroduodenostomy group of 35 patients averaged higher blood levels and lower fecal losses of fat than did the group of 58 patients who had gastrojejunostomy. Weight changes in these patients showed a general correlation with the measured alterations in fat digestion. Their study supported the concept that a gastroduodenal anastomosis offers a greater nutritional advantage than a gastrojejunostomy after otherwise identical gastric surgery.

One of the most baffling problems in gastrointestinal tract surgery, i.e., localization of unexplained hemorrhage, has been tackled by two

groups of investigators utilizing radioactive materials to aid in determining the site of bleeding. Ariel injected radioactive chromium intravenously after the insertion of a double lumen tube into the esophagus and stomach with a balloon inflated at the cardia. Samples of gastric and esophageal contents were then withdrawn and analyzed for radioactivity. In 25 patients the site of bleeding was found in the esophagus in 8, within the stomach or duodenum in 12, and the test was inconclusive in 5 patients. This test was advocated for use in patients with acute massive gastrointestinal hemorrhage.

Healey, Riggins, White, Habif, and Stewart reported an ingenious modification of a Cantor tube constructed with three small Geiger counters spaced at 8 inch intervals within the lumen of the tube. Each counter was connected to a separate count rate meter. In dogs, the tube was advanced into the stomach, small intestine, or colon. The animals were injected intravenously with radioactive phosphorous-labeled red cells. Single or multiple sites of hemorrhage were then produced in the alimentary tract and accurately localized by the increased counts obtained. Differentiation of radioactivity of blood in the mucosa from intraluminal blood apparently has not been a problem, although further experience with the technique will be necessary to establish the fact that radioactivity from two sources can be clearly distinguished in patients with unexplained gastrointestinal tract hemorrhage.

Several studies, which are of considerable practical importance if further clinical confirmation is forthcoming, were concerned primarily with the function of the intestinal tract and the intestinal contents. Redfern, Close, and Ellison studied the fluid and electrolyte loss into the obstructed ileum. Their findings indicated a rapid reabsorption of fluid from the lumen of the bowel after release of the obstruction. On the other hand, if fluid was aspirated from the bowel at the time of release of the obstruction, there was additional fluid and electrolyte loss into the bowel lumen during the postoperative period. Their findings would imply that, in general, such fluid should not be removed, or, if removed, increased replacement requirements should be anticipated.

A method of preventing postoperative adhesions by the intraperitoneal injection of fibrinolysin was presented by Spagna and Peskin. After standardized mechanical trauma to the cecum, the abdomen was shown to be free of adhesions in 18 of 20 rats treated with intraperitoneal fibrinolysin. Dense intraperitoneal adhesions were present in all control rats. No impairment of wound healing was noted. The difference in activity of various fibrinolytic preparations and different "lots" of the same preparation have been commented upon several times during this meeting and should be stressed.

Skin digestion about intestinal fistulas was prevented by the use of a preparation reported by Richardson and Purdy that contained 20 per cent ion exchange resin, 20 per cent zinc oxide, and 60 per cent hydrated petroleum. The application of this fundamental concept to the solution of a practical clinical problem is intriguing.

The control of peritoneal implants at the time of cancer resection has been of considerable interest in recent years. Atik, Massari, and Cohn found clorpactin less effective than saline in the prevention of tumor implantation of the Brown-Peirce tumor in the peritoneal cavity of the rabbit. A considerable mortality attended the use of clorpactin. McDonald, Gines, and Cole found the use of a 0.5 per cent solution of sodium hypochlorite to be the most effective of the solutions which they tested. Cameron and Knoernschild applied diagnostic cytology to the evaluation of lesions of the colon. They studied mucus removed by swabbing the mucosa of the rectosigmoid during sigmoidoscopy. The method was accurate in over 90 per cent of the cases in diagnosing tumors and disease. The exhibit of Ackerman, McFee, Santoro, and Wangensteen demonstrated their new technique of detecting gastric cancer by the method of in vivo radioautography. The technique is based on the selective absorption of radioactive phosphorus by gastric cancer in concentrations 50 to 500 per cent greater than by continguous normal gastric tissue. The material so concentrated is detected by its action on the emulsion of a coated gastric balloon. In clinical tests on 43 patients, the technique has been as accurate as conventional roentgen-ray examination and has at times correctly diagnosed lesions misdiagnosed by conventional diagnostic methods.

Fascinating studies in autoimmunity as a cause of ulcerative colitis were presented by LeVeen, Calem, and Falk. Thal reported on the occurrence of pancreatic antibodies in various diseases of the pancreas and the nature of

the pancreatic antigen. LeVeen and associates prepared an antiserum to dogs' colons by injecting a homogenate of canine colonic epithelium into rabbits and ducks. The serums from immunized animals when injected into normal dogs produced an immediate bloody diarrhea and, in some animals, a chronic disease with diffuse hemorrhagic ulceration of the mucosa which persisted as long as 8 months after the injection. Similar procedures in guinea pigs did not produce this disease. Thal found pancreatic antibodies in 32 of 36 patients with chronic pancreatitis, in 9 of 12 patients with carcinoma of the pancreas, and in 6 of 7 patients with cystic fibrosis of the pancreas. The antigen is water soluble and appears to be derived from the cytoplasmic reticulum.

Since the introduction by Roytt in 1956 of the hypothesis of autoimmunity to thyroglobulin as an important etiologic factor in chronic thyroiditis, this mechanism has been suggested as a possible factor in the etiology of a number of unexplained disease processes. The idea, supported by these previous experiments, that autoimmunity may play an important role in the etiology of chronic ulcerative colitis and chronic pancreatitis is an important concept which needs further study. The theory cannot be accepted as established. The evidence at present is insufficient.

Attempts to elucidate the known clinical association of alcoholism and pancreatitis have been presented by two groups. Walton, Schapiro, and Woodward studied changes in flow of pancreatic juice in dogs produced by intravenous secretin, histamine, and alcohol, and by oral alcohol. Similar observations were made after total gastrectomy. Only secretin was found to act directly upon the pancreas. Histamine and alcohol by oral and intravenous administration stimulated pancreatic secretion indirectly by stimulating gastric acid secretion which, on passage into the small intestine, caused a release of endogenous secretin.

McPhedran and Lucas found that dietary deficiency was more deleterious than alcohol to the liver and pancreas of rats. Alcohol at the dosage used in their experiments played no part in the production of pancreatic lesions.

Nabseth, Nicholson, Newman, Tose, and Reif found that, although intragastric cooling in animals with experimentally produced acute pancreatitis lowered amylase and lipase levels in the blood and peritoneal fluid, it failed to alter significantly the morbidity or mortality of the process. They suggest from these studies that the "lethal factor" in acute pancreatitis may not be enzymatic in nature.

The importance of bacteria in the fatal outcome of experimental bile peritonitis and the protective action of penicillin in this condition has been well documented in the results reported by Shelby, Cotlar, Massari, Atik, and Cohn.

A number of interesting studies concerning the hemodynamics of the portal and hepatic vascular systems have been reported. Cincotti, Welch, Carter, Cleary, Boba, and Nelson found that a 0.1 per cent arfonad intravenous drip produced a prolonged, predictable, and large fall in portal venous pressure in prohibitive surgical risk cirrhotic patients with bleeding varices. Pituitrin administered alone or in conjunction with arfonad was unpredictable in its action and at times actually increased portal pressure. In patients with ascites the removal of ascitic fluid lowered the portal pressure 1 centimeter of saline for each liter removed. Baber, Chafizadeh, Halligan, and Leevy also attempted to evaluate the effect of pituitrin on the portal venous pressure of 18 patients with cirrhosis. Pituitrin occasionally reduced portal pressure; more often it decreased blood flow without affecting wedged pressure. Splanchnic vasoconstriction presumably accounted for reduced blood flow, but vasomotor adjustments prevented a drop in intrasinusoidal pressure.

Harris and Schwartz in their studies of the effect of pitressin on hepatic oxygen tension concluded that pitressin was a generalized vasoconstrictor affecting the hepatic arterial circulation, but acting upon the splanchnic arterioles to a greater extent. The hepatic and portal flows are reciprocal, and even a temporary decrease in portal venous flow is accompanied by an increase from the hepatic arterial system.

The improper functioning of this delicate balance of the constrictor effect on the hepatic and splanchnic arteriolar systems in cirrhotic patients may explain the inconsistent effect of pitressin on portal venous pressures in cirrhotic patients, as indicated in other current reports. Using the same technique to measure hepatic and renal oxygen tension, Hinshaw, Pories, Harris, and Schwartz found microdextran to be the most effective plasma expander in its ability to increase oxygen availability to the tissues.

Therefore, they concluded that as a temporary plasma expander, it was preferable to dextrose with a larger molecular weight.

Studies of various types of shunting procedures and their effect upon portal and hepatic hemodynamics in both normal and cirrhotic subjects continue to add to our knowledge in this important field. Heer, Silvius, and Harper found that portacaval transposition and end-to-end or side-to-side portacaval shunts served to reduce portal pressures in dogs with cirrhosis. Liver blood flow and hepatic function were found to be reduced after either type of shunt procedure, but not with portacaval transposition. Mulder and Murray, by placing catheters in the radial artery, the hepatic vein, and through a side-to-side portacaval anastomosis in patients operated upon for bleeding varices 1 to 7 years previously, concluded that the side-to-side shunt provided a second route of exit for hepatic arterial blood partially blocked by the hepatic venous obstruction of cirrhosis. Also, they concluded that the blood so shunted passed through the hepatic parenchyma at the cellular level, aiding in its nutrition and metabolism.

Margulies and Welch presented evidence to indicate that side-to-side portacaval shunts protected dogs against the formation of ascites after the production of almost complete hepatic vein obstruction. They believed that this evidence supported the continued use of side-to-side portacaval anastomosis in the treatment of ascites secondary to hepatic cirrhosis.

Since Clarke, in 1958, called attention to the occasional occurrence of peptic ulceration in man after portacaval shunts and to the increased secretion in gastric pouches of dogs after these shunting procedures, a number of investigators have attempted to isolate the factors involved in this phenomenon.

O'Sullivan, Cantlin, Sweeney, Rosteing, and Foster found that removal of the rest of the stomach did not reduce the hypersecretion of the gastric pouch. Cornish, Silen, Eiseman, and Woods also presented evidence to indicate that gastric hypersecretion after portacaval shunts is an accentuation of the intestinal phase of gastric secretion. Contrary to these findings and to the results of Clarke and others, Castaneda, Griffen, Nicoloff, Leonard, and Wangensteen presented data which indirectly support the appealing contention that there is antral hyperfunction attending portacaval shunts and that greater gastrin activity explains gastric hypersecretion.

The majority of evidence to date would suggest that this hypersecretion is due to the liberation of histamine or a histamine-like substance. Its site of release remains in doubt but is probably in the intestinal tract.

Kukral, Kerth, and Cromer, in their studies of protein synthesis in the dog after total hepatectomy, found that one-third of the intermediate globulins and all of the gamma globulins are formed extrahepatically. Practically all albumin and fibrinogen synthesis occurs in the liver. Such findings are of interest to those who have attempted to circumvent the homograft reaction by performing total liver transplants.

The ultimate in abdominal visceral transplantation was performed by Starzl and Kaupp who homotransplanted the liver, stomach, omentum, spleen, pancreas, small intestine, and colon in 19 dogs. Massive entrapment of blood in the graft occurred regularly after completion of the vascular anastomosis. Maximum survival was 9 days. Some evidence of negative graft reaction was seen in the lungs and bone marrow.

The numerous investigators who have made so many noteworthy contributions to our knowledge in the field of gastrointestinal and biliary tract surgery during the past year must be complimented.

NEUROLOGIC SURGERY

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INTEREST continues in the physiology of the nervous system. This concern is manifested by a restless probing of the significance of the mesencephalic-thalamic junction, by speculation in the physiologic realm of profound hypothermia, and by a true spirit of inquiry into some new form of tumor therapy other than the socially accepted one of tumor resection. The stimuli for such diffi-

cult investigations stem from varied sources. In the first place there has been and always will be a valid tradition in neurologic surgery that expresses itself by the exploration of basic neurophysiology. In the second place, the conceptual patterns of sciences allied to physiology, that is biochemistry, pharmacology, biophysics, and microbiology, have become reasonably well established, and these concepts may now be applied with some degree of certainty to perplexing neurosurgical issues. Finally, the neurosurgeon himself has changed. Armed with an exquisitely refined technique and supporting armamentarium, he still treats patients very well indeed but beyond this has developed a growing and realistic spirit of investigation.

For 25 years, Loyal Davis and his students have studied the treatment of essential hypertension by a combination of thiocyanates and sympathectomy. Other and more sophisticated pharmacologic preparations and modern endocrinologic techniques have allowed them to examine basic principles a step further. Perhaps even more to the point are the studies on chronic stress by Kell and his group that parallel the work done on chronic stimulation of the hypothalamus and the production of various lesions in the gastrointestinal tract. Their work indicates that chronic stimulation of the cerebral vasomotor centers may induce sustained elevation of systemic blood pressure and pathologic changes in both coronary and peripheral vascular systems. In a world of continuing and expanding environmental stresses, the importance of the central nervous system in the genesis of such disorders is re-emphasized.

Be he scientist or therapist or fortunately both, the neurosurgeon must respond to some degree to the altering social scene and to its attendant social responsibilities. In this context, and for other reasons, the aging brain occupies a position of focused attention at this present time period in our history. Two study groups have described the complex physiology of parkinsonism, and others related the importance of subcortical regions in the genesis of motor responses and the topographic organization of memory. The focus of epileptogenic activity was again surveyed. The pharmacologic production of tremor, the changes produced by lesions in specific nuclear areas, the ability objectively to measure motor disorders and single cell responses to stimulation by drugs and more traditional means, and above all the growing concept that parkinsonism is a systemic disease are evidence of a growing maturity in the solution of this problem. Many references have also been made that relate the principles of blood coagulation, and its therapy, to the generic issue of cerebral thrombosis.

Few adventures of the mind have titillated the imagination of neurosurgeons more than theories having to do with the pathologic physiology of profound cerebral hypothermia. Five study groups have reiterated established facts and surgical techniques and have moved on to more refined areas of study, such as that of local brain stem cooling. The time appears apt for laboratory investigations in the areas of the pharmacologic control of cardiac arrhythmias, of the specificity of factors leading to neuronal injury, and of the oxygen tension of brain cells, to name but a few. The human application of induced cardiac arrest and cerebral ischemia is very intriguing and, when all conditions are known, will represent a new high point in neurosurgical endeavor.

Since Cushing's time, neurologic surgeons have regularly renewed their interest in an understanding of malignant brain tumors, usually by the means of adding a fresh approach to therapy. In the 16-odd years of the atomic age, this renewal of interest has dedicated itself to an understanding of those organic chemicals derived from mustard gas, to the general area of antitumor substances, and to the use of isotopes. By fortunate coincidence, vascular physiologists have been concerned with isolated brain preparations at the same time, under conditions of hypothermia, normothermia, and hyperthermia. These practical physiologists have studied unilateral cerebral circulation, surgical technique, the distribution of labelled antitumor substances, and a host of other matters. Typical of the spirit of unrest and inquiry in this field is the study by Ojemann and Brownell that combines isolated brain perfusion with the versenate compound of zinc 69. There have been few ventures in the history of neurosurgery that have opened more avenues of purposeful research than does that of isolated brain perfusion. There is much new in the field of neurosurgery and that is the way it should be.

OBSTETRICS AND GYNECOLOGY

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THE DISCIPLINE of the combined field of obstetrics and gynecology which so long has been associated with interesting clinical advances now has become a very rich area for more basic investigation.

An example of an important penetration of basic methodology is that by Swartwout and by Dietrich, Miller, and Hamilton. They have developed a modification of glass paper chromatography which is rapid and accurately quantitative for the measurement of steroids and lipids in samples containing less than 0.5 microgram. This is especially significant in the field of obstetrics and gynecology in which definitive progress has been slow in reproductive endocrinology because no practical method has been available for quantitative measurement of small amounts of steroids and related substances in body tissues and fluids.

Placental perfusion is being continued. Krantz has apparently solved some of the vicissitudes brought about by a difference in pressure between the fetal and maternal portions of the circulation.

Page believes that he has shown that estrogens and progesterone are synthesized in his placental preparation. For years it has been strongly suspected that there is a reciprocal relationship between chorionic gonadotrophin and the sex steroids in certain clinical conditions such as toxemia of pregnancy. Page may now be able to show whether or not this is true under rigidly controlled conditions.

Lin has shown that placental tissue may survive as long as 50 days when transplanted within millipore chambers. This exceeds all previous experiences since control homograft transplants usually disappear completely within 10 to 20 days. Andresen, Hass, Madden, and Papadopoulos reported further developments in their investigations of host homograft interactions during gestation. They have shown that homografts of muscle and fascia in pregnant rabbits exhibit signs of normal healing, whereas within 4 days of interruption of pregnancy typical and classical inflammation and angiitis and other homologous tissue reactions develop as usual. On the other hand, in pregnant rabbits who receive transfusions of fresh leucocytes, all homografts are rejected, much the same as in the nonpregnant individual. Thus, the reaction of the pregnant animal may be changed to that of the nonpregnant. It is quite possible that some of the key answers to the difficulties in transplantation of tissues may come through investigations carried out during pregnancy.

Several new techniques of importance in research were reported. Hutchinson, Hindle, and Westover have described a method for hypophysectomy in utero in guinea pigs, which shows promise of being an important tool with which to work in relation to studying fetal-maternal endocrine relationships and other aspects of intrauterine growth and development in the planning of fundamental experiments. Landy and his associates have developed a practical method for germfree delivery by hysterectomy in guinea pigs. Another technique of significant implication in the field of experimental embryology is that of Franklin and Brent. By interrupting uterine blood flow with a series of clamps at various stages of gestation in the rat, congenital malformations may be produced. The relatively long periods of time in which several embryos can be isolated from uterine blood flow appear to open up numerous possibilities for the study of fetal-maternal physiology.

Toxemia of pregnancy remains as one of the great enigmas in all of medicine and still is one of the 3 great causes of maternal mortality. It is encouraging to note, therefore, that promising research is being carried out in this field. Ringrose suggests that the mind may play an important role in the genesis of pregnancy toxemia. In an attempt to show this, he employed the Minnesota multiphasic personality inventory (M.M.P.I.) as a reputable personality test. This was given to a group of unmarried mothers in a Salvation Army Hospital. Of those in whom full-blown toxemia developed, 75 per cent had personality defects, whereas only 32 per cent were defective in those in whom toxemia did not develop. It was the belief that patients with abnormal personalities do not handle stress as ef-

ficiently and toxemia is apt to develop on the basis of vasoconstriction and other aspects of the pathophysiology of this disease.

On the other hand, Hunter has reported the finding of a pressor substance in the amniotic fluid, in decidua, and in the blood plasma of toxemic patients. He calls this substance hysterotonin. It is not found in normal pregnant women or in those with essential hypertension. Hysterotonin was also found in large amounts in the decidua of patients with hydatid mole who exhibited signs of toxemia. Most intriguing from the clinical point of view is the fact that removal of amniotic fluid, with reduction of uterine hypertonus, may bring about a drop in the elevated blood pressure. Furthermore, it was demonstrated that immediate postpartum curettage of the uterus in these eclamptogenic patients caused an amelioration of hypertension within 4 to 12 hours. This finding was believed to be due to the removal of the hysterotonin-rich decidua. If this work is confirmed, it may well be the most important ever done in toxemia of pregnancy and could lead to the saving of the lives of many young mothers.

Hon has developed a transistorized fetal heart monitor which provides an audible tone and flashing light and which records permanently the fetal heartbeat. The patient's movements and uterine contractions do not interfere with this recording. It is devised especially for the monitoring of patients in late labor and during delivery. Theoretically, this instrument may help eliminate the errors associated with sporadic auscultatory checking of fetal heartbeat and thereby add further to our ability to pick up instances of fetal distress and treat them promptly.

Piasecki, Egdahl, and Jackson have studied the rabbit fetus in utero with implanted fetal electrocardiograph leads. They report significant changes in fetal electrocardiograph tracings with maternal administration of nembutal or epinephrine. This method opens a broad avenue for physiologic and pharmacologic investigation of maternal-fetal relationships.

In the often disappointing area of infertility and sterility, several studies show promise. The surgical therapy of fallopian tube occlusion has been notoriously poor. Charles, Labes, Cohen, and Shoemaker have devised a new technique for replacement of a fallopian tube using segments of isolated ileum. This method is similar to the Bricker conduit. The segment, with its blood supply intact, is dissected so as to strip away mucosa and submucosa. It is then rolled over so that the serosal surface becomes the lining. This is placed over a polyethylene tube and is sutured into the open cornu of the uterus and endometrial cavity. It has been shown that the graft may persist intact and the lumen of the graft remain patent. In some of the 22 dogs operated upon, the lining serosa has been replaced by stratified epithelium. It remains to be seen whether pregnancy can be achieved.

Mann and McLarn demonstrated the important role of the uterine isthmus in cervical incompetency, which may be the cause of habitual abortion especially in the midtrimester. Radiopaque substances are injected into the uterus and, under fluoroscopy, the abnormally dilated isthmus or internal os of the cervix or both are well visualized. These studies have aided them in the placement of polyethylene-encased sutures circumferentially about the cervix beneath the mucosa to correct the defect. This operation has been performed on 50 women in the nonpregnant phase (in contradistinction to the Shirodkar operation), and 25 of these patients have become pregnant; 22 have had normal, full-term infants.

One of the most distressing causes of sterility has been the lack of ovulation in some women. Through the years, all attempts to produce ovulation, no matter what has been used in the human, have been unsuccessful. Recently the work of Gemzell and his associates has been confirmed by Buxton, and apparently ovulation may be produced now in a high percentage of patients with repeated doses of human pituitary gland preparation. The best results are obtained when a sequence of human follicular stimulating hormone and chorionic gonadotrophin is used.

Phlegmasia alba dolens constitutes a serious complication of pregnancy which, although rare, may be immediately fatal from pulmonary embolism or subsequent debilitation through the development of a postphlebitic limb. Earlier methods of anticoagulation alone or vein ligation and vein excision will usually prevent embolism. Haller has shown that immediate thrombectomy in these patients constitutes an important means of reconstituting function in the thrombosed iliofemoral veins. He believes that these patients should also have full anticoagulant therapy during and after the operation.

In the realm of female pelvic cancer, a number of new ideas have been brought forward. We have been disappointed in chemotherapy by perfusion in the female pelvis. There is a tremendous leak of the agent being used into the general circulation because of the rich collateral circulation present. Prout and his associates have been able to improve perfusion by more careful isolation of the pelvic circulation in dogs, and it is hoped that it will be possible to utilize some of their ideas in the human being.

Important experiences have been reported in radical surgery in cancer of the cervix. Here the removal of the vagina and the frequent fistula formation in association with the radical abdominal operation have been especially disconcerting. Along this line, Pratt has devised an operation for the lengthening of the partially removed vagina by isolating a segment of the sigmoid and swinging it over and attaching it to the wall of the shortened vagina. This has worked very well in his experience and provides quite normal lubrication.

It has been our practice to save ovarian tissue in situ with its blood supply in young women with invasive carcinoma of the cervix. Metastasis from stage I lesions to the ovary are almost nonexistent and the survival statistics when these organs are preserved at the time of radical surgery has been encouragingly high. Levels of follicular stimulating hormone (FSH) in these patients are normal, confirming that ovarian function continues normally even after the most extensive type of hysterectomy. This method may circumvent not only acute symptoms of the climacteric and the local anatomic distortion of premature genital senility but also fundamental metabolic aberrations, such as the early development of coronary atheromatosis.

The fistula problem with radical surgery is a tremendous one; an incidence of some 10 to 20 per cent of ureterovaginal fistulas and vesicovaginal fistulas is reported by most clinics. In a group of radical vaginal operations, in which the ureter is exposed from below rather than from above, the incidence of such fistulas has been lowered to approximately 1 per cent. Furthermore, at least as much parametrial tissue is removed with these operations as with the radical abdominal procedure.

It would appear that the rapid development of research potential in departments of obstetrics and gynecology augers well for the future. It is certain that we may look forward to increased numbers of significant reports on obstetrics and gynecology year after year.

PLASTIC SURGERY

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PLASTIC SURGERY is a specialty of methods which is not confined to anatomic boundaries and has a special, but by no means exclusive, interest in 4 phases of fundamental surgical problems: i.e., wound healing and infection, trauma and cancer of the head and face, burns, and tissue and organ transplantation.

Wound healing and infection. Analysis of the wound healing process continues. Darin, Wiviott, Maynard, and Frackelton evaluated the healing of rabbit wounds by fluorescent staining with acridine orange which stains the desoxyribonucleic acid bright green, the ribonucleic acid yellow-orange to red, and the surrounding muscle and connective tissue yellow-green to green. Intracellular ribonucleic acid is distributed adjacent to the incision during the first few days and the extracellular connective tissue stain appears about the fifth day. Maximum intracellular concentration within the wound itself occurs on the fifth to the tenth day. The extracellular components gradually diminish by the twenty-first day at which time the fluorescence is limited to the cytoplasm of the tissue cells adjacent to the wound. This graphic histologic study dissects the process of wound healing in a decisive manner.

Testing for a relationship between acute local inflammatory response and the subsequent reparative process, Freihoffer, Robinson, Jackson, and Dunphy found that the systemic injection of bacterial endotoxin accelerated the rate of col-

lagen synthesis in recently excised wounds at the twelfth day and the total amount of collagen at the twentieth day. Endotoxin injected locally was also effective. However, the increase in collagen deposition did not increase wound tensile strength, the latter being dependent on the degree of cross-linking of the collagen macromolecules extracellularly.

Another study of collagen was by Peacock who tested the mechanism of an in vitro system in rats. In vitro, certain amino acids and low molecular weight ions can influence the rate of heat precipitation of fibrils from cold and neutral salt solution of collagen. Testing the tensile strength of wounds in both the cellular phase at 7 days, and the collagen productive phase at 11 days, a decrease in tensile strength and in the total amount of extractible collagen occurred if the animals were fed additional urea, lysine, and thiocyanate. However, no beneficial effect on tensile strength resulted from the addition of any of the accelerators of the heat gelation process. Discussers mentioned the need for the study of wound healing in the human, and it was urged that all interested surgeons submit hypertrophic scars and keloids to basic investigators within their own institution.

These 4 studies, one a refined histologic study, 2 studies of collagen deposition, and the fourth a study of the effect of dietary trace element are difficult to integrate into a unified pattern. The feeling persists that the complicated processes of wound healing will continue to be studied individually, and not until more data have accumulated from all phases of the study will a unified pattern be discernible.

Forward and Cowan presented a concise study of tendon-to-bone suturing in rabbits, indicating its superiority over direct tendon-to-tendon suture. The direct tendon-to-bone suture heals somewhat as a fracture does with a rapid return of tensile strength after the 21 day period of immobilization with less late separation occurring 6 to 8 weeks later after resumption of motion.

Deformities of the head and neck area resulting from accidental trauma or from the treatment of cancer. Brown restressed 4 functions to be restored after facial injuries: i.e., the eye to see, the nose to breath, the mouth to eat, and the face to look normal. The importance of early repair of facial injuries and the value of seat belts in minimizing and preventing injuries from automobile accidents were stressed. Anderson's exhibit on the treatment of fractures of the jaw emphasized the need for general surgeons to interest themselves in the direct wiring of jaws and the handling of facial fractures because in no other traumatic injury is the final result so dependent upon early, adequate care.

In advanced cancer of the head and face area, a panel headed by McCormack described an aggressive approach to the surgery for cancer. Many patients, who otherwise were doomed to a prolonged and painful death, were salvaged by a planned, aggressive surgical approach for cancer of the jaw, tongue, and hypopharynx. Many of these patients were irradiation failures. None of the panelists believed that immediate reconstruction was imperative in every instance, but all thought that the urgency for repair should be judged according to the type of the neoplasm, the likelihood for arrest of the cancer, and the attitude of the particular patient.

Marchetta, Sako, and Creedon demonstrated in the dog a technique for the repair of cervical esophageal defects up to 4 or 5 centimeters in length by rotation of local pedicle flaps. A narrow strip, 1.5 centimeter in width, was able to tube itself to reconstitute gastrointestinal continuity. Microscopic study after several months revealed continuous contraction of the scarred area and stretching of the residual muscularis with maintenance of adequate patency of the lumen. This is experimental analysis of a clinical observation that even a small strip of cervical mucosa may become functional if covered by healthy tissue.

Beall, Harrington, Usher, and Morris reported the use of a marlex mesh for circumferential replacement of the dog trachea. The surprising finding was the lack of an air leak in these dogs. Marlex may be useful in the repair of tracheal defects caused by neoplasm, or as a splint for the trachea or larynx after traumatic fracture.

Burns. Metabolic and technical advances have lessened the morbidity but have not decreased the mortality from severe burns. Early excision of all burn tissue followed by skin grafts, either autograft or homograft, is the most logical way to try to decrease mortality. Cramer, Carroll, and McCormack have reported the systematically progressive excision and grafting in patients with potentially lethal burns. Taking advantage of the "golden period for grafting,"

the major portion of the burn wounds are replaced by healed skin grafts within 21 days, thus avoiding major skin grafting later when delay in healing occurs. Systematic excision and grafting are started as soon as the respiratory and metabolic aspects of the burn allow, usually by 7 days. A budget is set up: no more than 20 per cent of the body surface is excised at one time, and anesthesia lasts no longer than 90 minutes. Three or 4 such operations by well organized teams will allow healing of the major portions of burn wounds by the twenty-first day. Three patients, aged 82, 79, and 63 years with a statistical 100 per cent mortality have been salvaged. The number of patients is limited, but the approach is a wise one for otherwise hopeless situations.

Impaired survival in burn patients may be on an immunologic basis. This possibility was analyzed by Albright and Berry who extracted skin antigens to test for autoimmune reactions of normal and burned skin tissues. Using 25 to 35 per cent burns in guinea pigs, approximately 50 per cent being lethal, skin extracts in water, water and carbon dioxide, molar sodium chloride, 1 molar sodium chloride and carbon dioxide, 1 normal citric acid, and 1 molar sodium hydroxide were prepared. Distinct differences in the extractability of normal and burned skin was noted with the different methods. The extracts were then tested for a direct Coombs' reaction with lymph node cells of burned and nonburned guinea pigs. The results are not clear-cut in this experiment, but the approach may also be worth pursuing relative to skin grafting late in the burn.

Tissue and organ transplantation. Studies in this rapidly growing field may be subdivided into 3 categories: those dealing with the survival of transplanted organs, those with preservation of organs, and those dealing with the immunology of homograft reaction. The technical aspects of heart transplantation were described by Lower and Shumway. With a technique involving anastomoses of the pulmonary artery, the aorta, and the common posterior atrial wall containing the ostia of the venae cavae, the pulmonary veins, and a ridge of atrial septum, they were able to achieve survival of the homotransplanted hearts for 21 days in 1 instance. Besides being a superb technical feat, this may offer the use of the heart as a large mesenchymal organ to be used as a test object for histologic study of the rejection pattern. With increasing evidence that homograft rejection differs with different organs and tissues, it would be worthwhile to study the effect of drugs and irradiation on the survival of total heart transplants. The massive organ homotransplantation of Starzl and Kaupp which included the total stomach, liver, pancreas, spleen, small bowel, colon, and omentum, survived for 9 days. Their intention to overwhelm the immune response of the host by such a massive transplant seems unlikely to succeed on theoretic grounds. Experience with parabiosis in which a whole animal may be considered as a transplant antigen indicates that one partner ultimately is capable of destroying the other by an immunologic rejection phenomenon.

Marshall, Crowell, and Sturgis demonstrated the ability of lymph nodes, protected within the millipore membrane, to continue to produce detectable antibodies in a homologous host. The antibody to the H antigen of the Salmonella typhosa was detectable for 30 days, and the residual cell type left within the chamber appeared to be a primitive form of lymphocyte. The antibody titers, however, were not so high or long-lasting as in the control isografts for reasons not manifested by this study. This system, however, utilizes a heterologous transplant: i.e., salmonella organism in a mouse, and may not be analogous to pure homograft systems.

The effect of the antimetabolite, 6-mercaptopurine, on skin and kidney homografts was reported separately by Hubay, Powell, and Holden and by Zukoski, Lee, and Hume. The former group found no prolongation of skin graft survival in rabbits, rats, mice, or guinea pigs after 6-mercaptopurine therapy to the host. They concluded that previous beneficial reports might have been due to the general debility of the animals so treated. The latter group, using the kidney dog homograft system, reported the survival of 1 animal on 6-mercaptopurine therapy for 66 days after renal homografting and bilateral nephrectomy, although the mean survival of all the animals' kidneys was increased by only 10 days. However, the encouraging observation was made that many animals died with normal blood urea nitrogen levels and a normal microscopic kidney pattern. Death in many of the animals resulted from 6-mercaptopurine toxicity although some dogs did have definite evidence of homograft reaction. Differences between these two reports might be related to the dif-

ference in the source of antigen (the kidney, an intravenous antigen, the skin, a subdermal one), the total amount of antigen, or the species involved. In recent years, it has become apparent that skin grafts and kidney grafts did not always follow the same pattern of survival even in the same host, and this difference might explain these results.

In a study of the storage of kidneys and of the reversibility of the homograft reaction, Balankura, Goodwin, Murray, and Dammin retransplanted dog kidneys from a temporary host back to the original donor after varying periods of time from 1 to 8 days. A homograft reaction which was extremely severe at the time of retransplantation was capable of continued improvement for a period of 21 days, and could ultimately become life-sustaining as a solitary kidney. In some instances, the interstitial plasma cell infiltration continued to increase 7 to 10 days after the kidney was returned to the original host, possibly a reaction of the original host to the homologous cells now residing in the kidney. These investigators concluded that the homograft reaction was not an "all or none" phenomenon as it has been commonly assumed. Instead, a certain degree of reversibility exists, during which time therapy might be beneficial.

The theoretic concern in clinical kidney transplantation that the kidney transplant itself may react against the host was studied by Wheeler and Corson. With pure strains of mice, free grafts of kidney slices from parental strains into F_1 hybrids, and from F_1 hybrids into parental strains were performed. The ability of the host to reject the graft was obvious in the F_1 hybrid into parent combination, but in the parent into the F_1 hybrid combination, the only condition in which a graft versus host reaction is possible on genetic grounds, no effect was noted. This study with suitable control material indicated clearly that, in the mouse, kidney transplants are incapable of reacting against their hosts. This result concurs with other current studies involving irradiation of the donor kidney, labelling the donor kidney or recipient animal with triturated thymidine, and the transplantation of kidneys in heavily irradiated humans.

Pierce, Meeker, Weiner, Weiner, and Varco studied the desoxyribose nucleic acid synthesis in lymph nodes of rats rejecting homografts and noted the peak uptake of radioactive phosphorus into the desoxyribose nucleic acid at 7 to 11 days at the time of the maximum rejection of the homografts. This is another indication of the active synthesis of protein going on in the regional homograft during the period of maximum homograft rejection by the regional nodes.

A study of organ preservation included a report on frozen parathyroid glands, subsequently used as autografts by Russell, Gittes, and Sparrow. Slow freezing of the glands in 15 per cent glycerol preserved parathyroid activity in a deficient rat; on removal of the graft, the deficiency state returned. The microscopic appearance of these preserved glands was essentially normal. The preservation could be carried out at −79 or −195 degrees C. The longest storage period tested was 78 days.

There were 2 reports of selective kidney cooling. Kiser, Farley, Mueller, Strobel and Hitchcock produced rapid intra-arterial parenchymal hypothermia by perfusion of a composite solution of autologous blood, low molecular weight dextran, procaine, and heparin solution. The solution was precooled to 1 to 5 degrees C.; the cooled kidneys were then excised, stored in a refrigerator for as long as 7 hours, and then replanted successfully as a life-sustaining transplant. This is a simplified technique which may prove useful in renal artery surgery or aortic arterial surgery involving the renal arteries. Cockett used a mechanical heat exchanger for 2 hour regional kidney hypothermia and has applied it both in the laboratory and to patients undergoing renal artery surgery.

Jacob and Webb continued their study on the cooling and preservation of canine organs. Using hydrostatic pressure, they supercooled hearts to −19 degrees C., at which point the heart appeared normal, grossly and microscopically. On transplantation to the neck, however, the normal electrical reactivity did not return.

Two advances in the technique of small arterial anastomoses were presented. Holt and Lewis described a sutureless method using teflon rings with fine pins inserted as phalanges. Two identical rings are made just large enough to fit over the end of the vessel. Evenly spaced pin holes are made, each ring receiving alternating pins. The vessel edge is inverted on the face of the ring by the pin and the 2 teflon rings fixed by alignment and pressure opposing the intima

and fixing it. This is an extremely simple and inexpensive device which has great potential usefulness.

Jacobson and Suarez performed vascular anastomoses under the dissecting microscope adapted for surgical procedures. They were able consistently to suture vessels of 1 to 2 millimeters in diameter without subsequent thrombosis.

Protection from the adverse effects of total body irradiation by bone marrow, spleen, and chemicals has been reported by many investigators. The subject is of interest not only to those studying tumors, but also to those studying the transplantation because of the radiation mimetic effects of drugs such as nitrogen mustard and 6-mercaptopurine. Lillehei, Longerbeam, Hilal, and Yunis demonstrated that splenic homogenates protect otherwise lethally irradiated dogs, whereas vascularized retransplants of spleen or lead shielding of the spleen could not. This surprising finding of the superiority of a cellular brei raises the possibility that humeral factors may account for some of the protective effect of the spleen. The possibility that the individual cells are able to seek out depleted sites in the reticuloendothelial system may also account for this difference.

Webb, Jacob, Stone, and Dunphy, using bone marrow inplants into spleen as a test system, demonstrated a remarkable resistance of bone marrow to direct irradiation. Ribs directly irradiated at 500 to 55,000 roentgens were examined at 6 weeks and demonstrated that the red cell, white cell, and platelet series were not completely inactivated until doses of 3,000 roentgens were reached. The plasma cell series, on the other hand, were not destroyed by direct irradiation until the 5,000 roentgen dose was used. This interesting finding again raises the possibility that irradiation may exert its deleterious effect on bone marrow by humeral toxins liberated in the course of the irradiation.

Three studies of nitrogen mustard toxicity are of interest to the homograft problem. Ross, Carberry, and Kraus protected animals against the nitrogen mustard toxicity by the systemic use of sodium thiosulfate; Demetz, Herter, and Evans tested the role of the spleen in the prevention of nitrogen mustard toxicity and demonstrated that splenectomy decreased to a limited extent the systemic toxicity of intravenously administered nitrogen mustard, whereas temporary exclusion of the spleen from the circulation, or the use of fragmented or homogenized spleen, did not offer similar protection. The report of Ryan, Lochridge, and Jackson was a study of the effect of colchicine as a priming dose prior to the regional perfusion by nitrogen mustard in the therapy for tumors. By increasing the number of mitoses after colchicine a greater therapeutic effect of nitrogen mustard was demonstrated.

Two other presentations warranted inclusion. The production of congenital anomalies by arterial interference of the pregnant uterus was reported by Franklin and Brent. By clamping the uterine horn of rats, series of congenital anomalies could be produced. This study related the type of deformity to the timing and duration of the uterine ischemia. The production of germ-free guinea pigs delivered by hysterectomy was reported by Landy, Yerasimides, Growdon, and Bausor. By this technique, germ-free animals can be provided to investigators interested in a study of burns, wound healing, and organ transplantation.

TUMORS

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THE CONTINUING INTEREST of surgeons and their younger colleagues in various modalities for the treatment of patients with cancer is impressive. Far from being confined to those which are purely surgical in nature, these investigations have explored wide ranges of physiology and chemotherapy which include 4 aspects of the subject: The association of viruses or activating substances with animal and possibly with human cancer; the results of clinical trials of new methods of cancer treatment; studies of the rate of spread of cancer cells and the effect of systemic

and local conditions on metastases; and the enhanced effectiveness of combinations of chemotherapeutic agents on cancer.

Viruses and activating agents, together with immunologic studies relating to cancer were the subject of several important studies. Grace, Millian, Mirand, and Metzgar gave further results of their continuing study of the effect of the use of extracts of human cancer upon young Ha Swiss ICR mice. They found that in 8 to 10 per cent of surviving mice injected with these extracts a variety of malignant tumors developed, about 90 per cent of them being cancer of the breast and the second commonest, a lymphosarcoma. Several other histologic types of tumors as well developed early in the normal life span of these mice. In contrast, in only 0.9 per cent of the mice injected with benign human tumor extracts did any tumors develop at all. There are two unusual things about these tumors; one of them is that they were not transplantable whereas many spontaneous tumors in the same strain of mice are, and the second is that in the control animals, if tumors developed at all, it was not until very much later on in their natural life span. Mixed visceral extracts of animals which had been injected at birth with extracts of human tumor were infective, and in 8 of 40 such trials, tumors also developed in the second generation animals at an early age.

Other than this, Grace and his associates have been unable to propagate whatever it is that they have been obtaining from a variety of human cancer. It does not seem to be transmissible by any of the standard techniques for the transmission of viruses. They are virtually certain from immunologic studies that it is not polyoma virus. It does not appear to be the Bittner mammary cancer virus, even though 90 per cent of the induced tumors are carcinoma of the breast, because it has not been transmissible to sensitive strains of animals. Whether it is a virus or an activating agent for some latent virus in the strain of mice they have been using, they do not know. No claim whatever is made for causal relationship with human cancer.

Sacks, Clark, and Egdahl studied another virus, one that causes an acute hemolytic anemia in rats. This is an infectious agent, it can be transmitted within the cage and even from cage to cage within a colony. It kills quite a number of the animals that become infected, but the survivors appear to have certain peculiarities. The first is that those that survive infection are significantly more resistant to the transmission by implantation of a wide variety of transplantable rat tumors. Either they are totally immune or there is a significant reduction in the percentage of takes when compared to controls of exactly the same strain of animals. The second observation is that in some of these animals, after a few weeks to 8 months, peculiar spontaneous tumors develop. These lesions range the gamut from apparently sterile abscesses and granulomas to and including histologically malignant adenocarcinomas of lungs, salivary glands, or abdominal viscera. These are odd tumors. They do not kill the animals; instead, they have gone through cycles of exacerbation and remission during the period of up to a year that they have been studied. What the nature of this agent is, why it should produce at least partial immunity to standard transplantable tumors, and why it should produce this variety of lesions from inflammatory to histologically malignant is not known; however, if lesions from animals which recovered from the anemia phase of infection are transplanted to normal rats the full gamut of lesions develops in the recipients but without the occurrence of the anemia.

Certainly among the most important papers in this group relating to viruses was the Martin Memorial lecture given by Wendell M. Stanley. Stanley, who is widely known for his research in the virus field, pointed out that there are 4 groups of investigators now who have isolated some kind of substance from human cancer which has effects on animals: Schwartz and his associates have shown that there is an agent in human cancer which accelerates the development of mouse leukemia; Grace's study has already been discussed; Stewart and Eddy have isolated an agent from human cancer as have Toolan, Moore, and Dalldorf. Toolan has found a replicating agent which can be passed from animal to animal and which in hamsters produces skeletal changes in the jaw and skull. This agent has been recovered from a variety of human cancers. Stanley spoke of the importance of our beginning knowledge of biochemical changes in the nucleic acid of cells produced by infective ribonucleic acid and desoxyribose nucleic acid and concluded with his own personal opinion that since a wide variety of animals has now been shown to have viruses as the cause of cancer, it is highly unlikely that we would not find

some ordinary virus which plays an important role in the etiology of cancer in man. He also, of course, stressed the point that there is yet no proof of viral cause of cancer in man.

The importance of collaboration among many institutions in the evaluation of the results obtained by alternative methods of treating human cancer was emphasized in several reports. Ian MacDonald, Chairman of the Joint Committee of the American College of Surgeons and the American College of Physicians which was set up to study the effectiveness of adrenalectomy and hypophysectomy in the treatment of women with advanced breast cancer, reported, as a part of a panel discussion on management of the patient with carcinoma of the breast, the results of the combined studies from 17 co-operating institutions. It is of considerable interest that the remissions of advanced breast cancer achieved by adrenalectomy and by hypophysectomy were so exactly identical that MacDonald commented that, if these results had been presented from one institution, most people would believe that the data had been highly biased or selected. For evaluation, it is important first to recognize that about one-third of the women who have recurrent or primary inoperable breast cancer and who have nonfunctioning or no ovaries respond to either hypophysectomy or bilateral adrenalectomy with remissions of 6 months or more in duration, and secondly that there must be a critical evaluation, not as yet accomplished, of the sequelae of both types of procedures. The mineral metabolism faults which exist when the adrenals are removed and aldosterone is no longer available to the patient, and the sequelae of diabetes insipidus and of loss of the sense of smell which are major complications of the hypophysectomy procedure both present problems of importance to patient and physician alike. Neither hypophysectomy nor adrenalectomy should be contemplated in premenopausal women until surgical oophorectomy has been performed and its effect on the recurrent breast cancer observed. Failure to respond to oophorectomy reduces, but does not eliminate, response to subsequent adrenalectomy or hypophysectomy. It is clear from MacDonald's report that the duration of life is significantly increased for those who respond to either adrenalectomy or hypophysectomy, averaging 22 months as compared to 7.6 months for those who failed to respond.

George Moore, Chairman of the National Committee on Adjuvant Chemotherapy in Surgery, reported results as they have been obtained by the study group utilizing adjuvant chemotherapy. He reported on two groups, one of which consisted of patients with carcinoma of the lung treated with nitrogen mustard at the time and immediately after surgery. The results in the control and the treated series are identical and, unfortunately, the natural history of lung cancer being what it is, enough time has gone by so that most of the patients in both groups are dead.

The results, however, in the second group, patients with breast cancer, are startling. There were 160 premenopausal and 430 postmenopausal women in the group reported. In the premenopausal women of the group treated with thiotriethylene phosphoramide (TSPA), 95 per cent have remained free of disease for 26 months, whereas 46 per cent of the control group remain free of disease. While this is an extraordinary difference, the figure of 46 per cent free of disease at 26 months after radical mastectomy seems quite low for a general average throughout the country even in premenopausal women. The 95 per cent free of disease in the treated group, with no recurrences so far beyond 7 months after surgery, certainly merits further observation. In the group of postmenopausal patients 89 per cent of those treated with TSPA along with surgery remained free of disease to 26 months, while 66 per cent of those in the control group are free of recurrence. In the total group, if the axillary lymph nodes were positive, 80 per cent remained free in the treated group and only 40 per cent in the control group.

One must bring the caution of a very short observation time into this report. We all recognize the fact that even 5 years' survival has no great significance in the ultimate prognosis of breast cancer, but certainly these early results are highly suggestive that in this particular setting in the particular disease, we may at last have something that will supplement our ability with surgery and radiation therapy to affect at least the immediate mortality of human breast cancer.

North, speaking on behalf of a group of 21 Veterans Administration Hospitals which have been carrying on a similar adjuvant chemotherapy program, noted that in their group there was no difference in the control and the treated

groups in cancer of the lung, stomach, or colon-rectum. He emphasized the very real dangers in the use of these toxic and powerful chemicals in conjunction with surgery. He pointed out that there had been serious complications and a considerable number of deaths in the treated group, and that this was believed to be due to overdosage in the initial group study done by the Veterans Administration Hospitals. It required reduction in a considerable degree of the amount of drug which was given before the patients were not immediately jeopardized by the treatment administered.

Despite the early encouraging results reported with patients with cancer of the breast treated at the time of radical mastectomy with TSPA, more time must elapse before the results can be considered significant enough for general use. It must be emphasized that the alkylating agents, of which TSPA is one, are powerful systemic poisons, and that in addition to their short range toxicity, the long term effects of their use in man is as yet largely unknown.

There has been a general reduction in the enthusiasm for the use of perfusion in treating regional cancer, with a continuing active interest in the method as a means of evaluating chemotherapeutic agents.

Creech, a pioneer in the field, described problems of leakage into the systemic circuit when using chemotherapy by perfusion. He stated that only in extremities was the leak kept to a reasonably low level, about 10 per cent in an hour of perfusion. If the iliac vessels were used, 40 per cent leak in 60 minutes was found; in perfusion of the pelvis a 60 per cent leak in 40 minutes, and in head and neck perfusion essentially a 100 per cent leak in 10 minutes. These facts, of course, limit the use of perfusion to highly active agents which act within a few minutes and, secondly, limit the total dosage which can be administered in order to protect the marrow and gastrointestinal tract of those being perfused. Some groups, for example, Herter, Markowitz, Price, Weissman, and Demetz have entirely abandoned perfusion and have gone over to attempting to treat regional cancer with intra-arterial infusion. This technique was initially described by Sullivan about 2 years ago and involves the placement of a small polyethylene catheter into the arterial supply to the area bearing cancer and the use of the longer acting chemotherapeutic agents by continuous infusion over a period of days and even a couple of weeks. Herter and his associates have been using methotrexate and 6-aminonicotinamide, both of which are antimetabolites and neutralizing these within the body by giving the normal metabolites, citrovorum factor and nicotinamide. In this way, it was hoped that a high concentration of antimetabolite in the area of the tumor would not affect the host; in preliminary experience with human cases they have found encouraging results. They have used a Barron pump designed originally for giving fluids or food through a nasogastric tube and find that the complex and expensive types of pumps originally described are not necessary.

Others, including Ross, Carberry, and Kraus, have attempted to put an antidote into the systemic circulation first and then do regional perfusion using nitrogen mustard, a rapidly acting agent. They found that its action could be blocked by previously administered sodium thiosulfate and that this agent, a practically benign one that has been used for study of extracellular fluid space for a considerable number of years, permitted the use of considerably higher dosage levels of nitrogen mustard within a regional area. However, caution must be expressed with regard to the use of these active agents for extensive local tissue destruction and peripheral nerve injuries have occurred with perfusion of extremities with alkylating agents.

The maximum tolerance of pulmonary tissue to nitrogen mustard perfusion was found to be 0.2 milligram per kilogram of body weight by Baxter, Goswitz, Pratt, and Klassen. They perfused the isolated left lung of dogs with varying doses of nitrogen mustard, and then determined pulmonary function after recovery as well as making histologic sections. Any dose above 0.2 milligram per kilogram of nitrogen mustard resulted in severe pulmonary damage, and there were no survivors of 9 dogs perfused with more than 0.4 milligram per kilogram.

Studies of the rate of spread of cancer cells and the effect of local and systemic conditions on the incidence of metastases provided interesting new information.

Fisher and Fisher showed that blocking the reticuloendothelial system with India ink or thorotrast increases the takes of Walker 256 carcinosarcoma in rats when the cancer cells are given intravenously to the Sprague Dawley strain. The interesting thing is that blocking the reticuloendothelial system before the injection

worked very well in reducing resistance, but it also worked if the India ink or thorotrast was given up to 24 hours after the tumor cells had been put in. This observation suggests that there is a period of time of at least 24 hours during which the cells are either circulating or not as yet imbedded wherever they are going to grow, and that the reticuloendothelial system plays a role in the rejection of those cells up to 24 hours after they are given intravenously.

Jonasson showed that viable tumor cells could be present in the heart blood of guinea pigs and of hamsters, and that in some instances these tumor cells did not implant because no metastases developed after the primary tumor, which had been implanted in the leg, was amputated. Moore, however, in commenting on this paper, stated that, in his experience, patients with circulating cells in the blood stream generally had a bad prognosis. He believed that this was in contrast to earlier reports by Engle who had stated that quite a substantial number of patients with circulating cancer cells had survived beyond 5 years without evidence of metastatic disease. Moore thought that differences in interpretation by cytologists of what actually constitutes cancer cells in the blood stream was probably responsible.

Fortner showed that one type of hamster melanoma metastasized within 2 hours of the time it was implanted in the hind leg of this animal. The experiments were done by amputating the entire implanted leg at varying times after implantation. It is interesting that if the leg were amputated in anything less than 2 hours' time, no metastases occurred but that metastases developed by 4 hours and were nearly 100 per cent with 6 hours' delay in amputation. This finding eliminates simple mechanical spread of the cells into the blood stream or the lymph during the process of injection. It suggests that there is some active process on the part of the implanted tumor cells that starts them through the blood stream and through the lymphatics.

Chan, McDonald, and Cole showed that, if rat livers were injured by carbon tetrachloride, many more metastases developed in them with intravenously administered Walker 256 tumor cells than in the controls. The existence of liver damage in patients with enhanced metastasis and the occurrence of primary tumors have suggested that the damaged liver is a more fertile site for the growth of metastatic cancer.

Olch, Stevenson, and Harkins showed that sometimes sublethal doses of roentgen-ray therapy increase the number of metastases in an experimental setting in animals. This observation was interpreted as being one more demonstration of the effect of stress as an agent in decreasing host resistance.

There is an increasing interest in the use of combinations of chemotherapeutic drugs in the treatment of patients with advanced cancer because of the demonstration of the enhanced effectiveness of such combinations under certain conditions. The report of Herter and his associates, utilizing methotrexate and 6-aminonicotinamide by intra-arterial infusion previously mentioned is an example. Li and his associates have treated chorioepithelioma metastatic to the lungs with combinations of 2 and 3 agents, an antimetabolite, an antibiotic, and an alkylating agent, with encouraging responses.

Curreri, at a panel on chemotherapy, spoke on the use of 5-fluorouracil and 5-fluorouracil riboside (FUDR). In addition, he showed a series of results, some of them in preliminary stages in which 2 and sometimes 3 agents have been used together. The effectiveness of these combinations seems to be somewhat greater than that of 5-fluorouracil alone, but 5-fluorouracil itself has given excellent temporary remissions in some patients with colon and breast carcinoma, recurrent or inoperable. However, Curreri quite properly warned that we still do not have any specific drugs for cancer cells. These agents are nonspecific and essentially hit rapidly growing cells, and therefore, they are all toxic to bone marrow and the gastrointestinal tract, in particular.

Ryan, Lochridge, and Jackson used an antitumor agent, colchicine, which many years ago was used to cause shrinkage of some cancers in man, with and without nitrogen mustard, to determine its effect on the Ehrlich ascites tumor in mice. Colchicine and nitrogen mustard together proved effective in sterilizing 20 per cent of the mice with the Ehrlich ascites tumor. Nitrogen mustard alone worked in only 2 per cent and colchicine did not prove effective. The synergistic effect of 2 drugs was nicely demonstrated.

Cooper and Goldring demonstrated some very interesting deleterious effects of various smokes and gases, including tobacco and cigarette smoke, on tissue cultures and on embryonic lung. Their unique method of assessing the effect of

these agents did not produce any carcinomas as such but did produce marked abnormalities in growth and arrest of growth with some smokes.

Thomas, Loken, Gordan, and Goldman presented a paper of clinical importance in which they showed that in 50 per cent of patients with breast cancer hypercalcemia had developed at some time. The importance of this finding lies in the fact that the hypercalcemia is often reversible by proper treatment with fluids and steroids and that, unrecognized, it results in an acute biochemical mortality. They reported that some patients survived 2 and 3 years after an attack of acute hypercalcemia with remissions induced by treatment. They pointed out that the serum calcium should be watched most carefully in patients who have recurrent breast cancer. In 15 per cent of their cases of hypercalcemia there was no evidence of skeletal metastases by roentgenographic examination. Anorexia, nausea, polyuria, and polydipsia are the common beginning symptoms of hypercalcemia and when these symptoms develop in patients with breast cancer their serum calcium should be checked at once. The lesion may be reversible and many months or years of useful living given to the patient.

Further evidence to suggest the ineffectiveness of chlorpactin XCB on the spread of tumors of the colon was presented by Atik, Massari, and Cohn. They demonstrated that in rabbits, seeding and growth of the Brown-Pearce tumor at colectomy occurred equally as frequently and perhaps more profusely when chlorpactin XCB 0.5 per cent solution was used to treat the peritoneal cavity as when an equal volume of saline was used. An exhibit by Cole's group, however, suggested that 0.5 per cent Dakin's solution was the most effective material in their experience in reducing wound implantation. It should be remembered that any presently known material that will kill cancer cells will also kill normal cells, and that any material that kills cells is toxic to the whole patient if enough of it is absorbed.

Moore, in discussing the present status of chemotherapy, said that "today we have a wide variety of ineffective drugs with which to treat cancer." To this could well be added that we have a wide variety of operations with limited success in treating cancer, even when it appears to be localized and operable. Neither of these facts, however, deters surgeons from trying to find better ways of treating patients who have cancer. In so doing they are contributing significantly to knowledge of the phenomenon of abnormal growth and factors which may play a role in its initiation and propagation.

UROLOGY

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In an ever widening attack on prostatic cancer, efforts are constantly being made in the experimental laboratory to identify mechanisms that regulate prostatic growth and also alter or destroy the growth already established.

Working in this latter direction Behnam and Hodges isolated the prostatic circulation in dogs and perfused the prostate with compounds of radioactive phosphorus, P^{32}, and with the antitumor agents, actinomycin D and 5-fluorouracil. The escape of these substances into the general circulation was negligible, and the uptake of radioactive phosphorus by the prostate was increased 3 to 10 times by oxygenation and was greatest when diethylstilbestrol was used.

To simulate a clinical situation in which less complete isolation can be achieved, some dogs were perfused after ligation of only the posterior division of the hypogastric vessels. The concentration of radioactive phosphorus in the general circulation was found to be only one-fourth that in the prostatic circulation, and the concentration in various viscera, one-fourth that in the prostate. The escape of this much radioactive material did not appear to harm these particular dogs. Other workers, however, who have tried visceral perfusion in patients are becoming concerned with the amount of leakage of the radioactive material into the general circulation.

The rare case of urinary incontinence that follows surgical relief of prostatic obstruction has continued to resist all measures to restore

urinary control. Occasional partial successes with a wide variety of techniques have been described from time to time, but the methods usually have been discarded later, as additional experience has found them wanting.

An experimental and clinical study of this problem by Goodwin, Cockett, and Martin has underscored the difficulties long known to urologists and has shown that a number of new and ingenious techniques although occasionally successful usually fail in the long run. After a thorough investigation of all conceivable aspects of this condition these investigators have concluded that no standard method of curing postoperative urinary incontinence in the male is yet in sight.

Pierce and Braun have shown by a clinical study of 17 adults that urinary flow ceases when it encounters a mechanical block in the form of intravesical pressure high enough to equal or exceed the maximum ureteral peristaltic pressure. This pressure ranges from 40 to 50 centimeters of water in the normal person and, when maintained in the bladder for 10 to 15 minutes, results in reversible hydroureter and hydronephrosis. These observations confirm the widely held view that cessation of urinary flow following acute, or marked, urinary retention is the result of usually temporary mechanical ureteral obstruction at the bladder level.

Another study of the effects of high intravesical pressure was reported by Schoenberg and Murphy, who had been concerned with its relationship to complications of endoscopic procedures. During these operations in 25 patients they had found intravesical pressure to range from 30 to 75 centimeters of water.

In 30 dogs they used a water suspension of finely divided carbon particles to raise the intravesical pressure intermittently from 0 to 40 centimeters of water for 1 hour.

In the control group, only edema of the periprostatic and perivesical tissues was found, with no infiltration of carbon particles. In the dogs previously treated by electroresection of the prostate gland, or by scooping out a small area of bladder wall with the electrocautery, carbon particles were found in tissue spaces or lymphatics deep in the tissues, along with periprostatic and perivesical edema. Schoenberg and Murphy believe this means that local and general dissemination of cancer cells or bacteria, as well as absorption of irrigating fluid, may take place when overdistention of the bladder occurs during endoscopic procedures. Overdistention therefore should not be permitted.

In any urologic practice there are always a few patients who return, or go elsewhere, because of a postoperative fibrous contracture of the bladder neck long after complete and satisfactory removal of the original obstruction. This condition may be seen at all ages and even in little girls. Campbell and Greene carried out suprapubic operations in 23 male and 9 female dogs to see which of 4 different types of operation upon the vesical outlet would produce the least contracture. Fibrous contractures developed in both sexes after simple excision with or without electricity, and even without the removal of any prostatic tissue. The only operation that did not result in contracture was the block excision of the bladder neck followed by vesicourethral anastomosis.

Two aspects of this study are worthy of special emphasis: first, the electrotome did not cause appreciably more contractures than did excision with the cold blade; and second, contracture does not depend on the removal of prostatic tissue, since it was produced simply by removing fibromuscular tissue. Contractures of the sort produced in these experiments, however, are not often encountered in clinical practice, and there is no need to abandon at present the standard procedures for relief of bladder neck obstruction.

A problem that has been especially troublesome is the re-establishment of the continuity of the ureter when its lower end has been damaged at a level so high that simple ureterovesical implantation is impossible. To avoid nephrectomy in such a situation, the short upper ureter has been dealt with in various ways, but all of the methods currently used have been unsuccessful at times.

Viek and Uhlman believe that they have found a still better method, consisting of a full thickness bladder flap, raised so as to bridge the gap, and left open, flat and unsplinted. To the upper end of this open flap is sutured the spatulated end of the short upper ureter. In a series of dogs, after raising this flap they closed the bladder defect and drained the bladder and peritoneal cavity for 10 days. Urograms and cystograms were made on the fourteenth day. In 9 of 10 dogs there was no extravasation nor hydronephrosis, and in the tenth dog the slight hydronephrosis had disappeared by the twenty-first day. Vesicoureteral reflux was absent in 8

dogs, and after 3 months had disappeared in 1 of the other 2.

These results are rather spectacular and suggest the remarkable ability of a flat flap of bladder to regenerate rapidly and form a tube which does not obstruct the urinary flow and rarely permits reflux to occur. The use of this technique in the case of 1 adult female patient gave an excellent result.

Much attention has been paid recently to the pathogenesis of pyelonephritis which has been reported to exist in 10 to 20 per cent of autopsy cases. Despite evidence that under certain circumstances bacteria can ascend through various pathways from a primarily infected lower urinary tract, Rattner and Braun believe that the hematogenous route to the kidney is the most likely.

They implanted coliform bacilli in the bladders in a series of dogs. One group had previously been prepared by being given intravenous injections of coagulase positive Staphylococcus aureus and a second group, by performance of a right cutaneous ureterostomy. Eighty-four per cent of samples of renal tissue examined bacteriologically 1 to 7 days later showed the presence of the originally implanted bacilli. This incidence was not affected by preliminary staphylococcal injections nor by cutaneous ureterostomy.

Rattner and Braun suggest that under the conditions of their experiment the route of transplantation of bacteria from bladder to kidneys was undoubtedly hematogenous since cutaneous ureterostomy provided no barrier. They also believe that results obtained in rats and rabbits do not necessarily reveal mechanisms that exist in man, since in their dogs the kidneys became infected without preliminary trauma.

In postoperative acute renal failure the first sign is diminished urine volume. This may result from acute dehydration, bilateral ureteral ligation, or parenchymal renal damage. In an effort to make an accurate differentiation of these conditions, Libretti, O'Conor, and Grayhack studied radioisotope renograms in 3 groups of dogs in which they produced acute renal insufficiency by dehydration, by ureteral ligation, and by acute tubular necrosis. When renograms were made within 48 hours the tracings obtained by ureteral ligation and by dehydration were identical and were strikingly different from those resulting from acute tubular necrosis. Rehydration, however, caused the tracings in the dehydrated dogs to return to normal but had no effect on the others.

This interesting study suggests that the radioisotope renogram in cases of oliguria or anuria, if employed early, may make possible the differentiation of ureteral obstruction from other types of acute urinary suppression.

Artificial kidneys have saved the lives of many patients with acute renal insufficiency by borrowing the time that is required for the healing of the acute renal lesions, but they are complicated and cumbersome and often take considerable time to set up after the emergency develops.

Moore and Lehman have developed a simple apparatus containing essentially a cation resin column and using an extracorporeal pump circuit, one tube of which is connected to the femoral artery and the other to the femoral vein. This can be primed with the patient's own blood and set up quickly to tide the patient over until the artificial kidney can be made ready. It cleared the blood and improved the electrocardiograms in 15 nephrectomized dogs and in 3 acutely ill patients, but Moore and Lehman are frank to admit that danger is always present, and constant supervision is necessary. Their apparatus is less complicated than artificial kidneys, and, because of the speed of operation, can be used to lower the serum K+ and improve the electrocardiograms while the artificial kidney is being prepared.

In renovascular hypertension the obstruction is not always limited to one large and accessible vessel but may be diffuse and intrarenal. To preserve such kidneys, especially when the process is bilateral, Glenn, Harvard, and Deming have attempted to establish a new intrarenal circulation in dogs by suturing an isolated patch of ileum, denuded of mucosa and submucosa, to a decapsulated area on the surface of the kidney. After occlusion of the renal artery, good peripheral vascular transfer was found histologically, and normal excretory pyelograms were obtained in all animals. There was some doubt in regard to an actual increase in glomerular flow, but there was some improvement in tubular function after the transfer. These investigators believe this method of transferring blood supply to the renal parenchyma is superior to other methods which have been tried, but success in the dog does not necessarily mean that the procedure will work in man. In 1940 Mason,

Robinson, and Blalock showed that adequate renal function and a normal intrarenal blood pressure could be sustained by collateral arteries from the ovarian artery in the dog, and Klapproth in a study of renal arterial circulation in the dog found a significant number of transcapsular collateral arteries in their specimens. Perhaps it is these unique vessels that made possible the transfer of blood supply in these experiments.

The length of time the canine kidney can withstand occlusion of the pedicle has been studied by Yoho, Stueber, Koletsky, and Persky. After recovery following contralateral nephrectomy, the opposite renal pedicle was occluded for 2 hours in 30 dogs. In one group the occlusion was continuous; in a second group the clamp was removed for 3 minutes at the end of the first hour; in the last group the clamp was removed for 3 minutes at the end of each half hour. With continuous occlusion the mortality was 70 per cent; with 4 half-hour occlusions, it was 40 per cent. In the group with 2 periods of 1 hour occlusion, it was only 10 per cent.

These investigators conclude that a 3 minute period of free flow dividing 2 one hour periods of occlusion provides the necessary oxygenation during the period of vascular release. However, when the pedicle is clamped 3 separate times, trauma to the artery and vein outweighs the advantage of increased oxygenation.

The mechanism of renal failure following aortic crossclamping below the renal pedicles is not fully understood. Seven of 140 patients suffered urinary suppression and 4 of these died in irreversible renal failure. Reports of infrarenal aortic clamping for 2 hours in dogs have been inconsistent and confusing, with distal tubular necrosis occurring in some but not in others, and apparently being prevented by arfonad infusion or by infiltration of the tissues about the renal pedicles with xylocaine.

Because of their clinical observations in the face of these conflicting reports, Chamberlain, Symbas, Foster, and Harris studied the effect of 2 hours of infrarenal crossclamping in 21 dogs. In 6 of these, renal blood flow was directly measured after a segment of vena cava, into which the renal veins drained, was isolated. In 5 additional dogs a similar venous shunt was established but the aorta was not clamped.

They found that the renal blood flow decreased between 10 and 30 per cent during the period of aortic occlusion and even after release of the clamp, but distal tubular necrosis did not occur in any of the animals. In the last group of 5 dogs, having the venous shunt but no aortic occlusion, the results were just the same. They conclude that reduction in renal blood flow is probably the result of nonspecific surgical trauma, and this reduction might be sufficient to cause renal failure in patients with pre-existing renal disease.

THE SURGEON AT WORK

THE TECHNIQUE OF SECURING THE BASE OF THE LEFT AURICULAR APPENDAGE AFTER MITRAL VALVULAR COMMISSUROTOMY

ELLIOTT S. HURWITT, M.D., F.A.C.S., and ALFRED A. ROSENBLATT, M.D.,
New York, New York

THE LEFT AURICULAR APPENDAGE affords the optimum portal of entry for the exploring finger in the standard mitral valvular commissurotomy. A previously placed purse-string suture around the base of the appendage may be snugged onto the intracardiac finger to prevent blood loss during the digital maneuvers. Hemostasis is secured when the finger is removed from the heart by one of two techniques: (a) ligation of the purse-string suture, frequently reinforced by a second tie of the same material, followed by amputation of the redundant appendage and oversewing of the line of resection; or (b) placing a clamp across the base of the appendage, excision of the excess, and oversewing the line of resection, discarding the purse-string suture if one had been used.

From the Surgical Division and the Henry L. and Lucy Moses Surgical Research Laboratories, the Montefiore Hospital, New York.

The theoretic advantage of the purse-string ligature technique is that this should afford the greatest opportunity for maximum elimination of the appendage as a possible nidus for the sequelae of thrombus formation and embolization. Possible objections would include wrinkling of the wall of the auricle drawn toward the ligature, with creation of crevices in which clots might form, and the heavy nature of the suture material. On the other hand, with the clamp technique one should be able to obtain a smooth auricular surface and to employ fine silk in closing the heart. However, a shallow groove of appendage must be left, corresponding to slightly more than the width of the clamp, and this might enhance the potential for clotting.

The practical importance of the problem is emphasized by two significant observations: (1) infrequently, systemic embolization has occurred both early and late after mitral valvular commis-

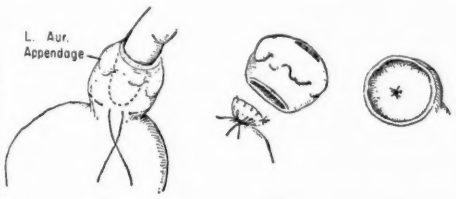

FIG. 1.

FIG. 1. Purse-string suture technique for securing the base of the left auricular appendage.

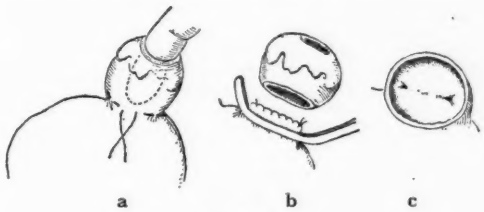

FIG. 2.

FIG. 2. The clamp and suture technique of auricular closure.

surotomy, irrespective of preoperative emboli; and (2) postmortem examinations, both early and late after mitral valvular commissurotomy, have occasionally disclosed organized mural thrombus at the site of the stump of the left auricular appendage, sometimes with embolism.

An attempt was made in the laboratory to determine which method of auricular closure was associated with the greater incidence of thrombus formation and which resulted in the most extensive ablation of the appendage. During the course of other experiments, a standard exploration of the mitral valve as in the clinical procedure was performed on 10 dogs. In 5 the purse-string suture technique was employed, as in Figure 1. The clamp and suture technique was used in the other 5, as illustrated in Figure 2. The dogs were sacrificed at intervals from 9 to 11 months postoperatively.

Thrombus formation at the suture line was not observed in a single instance. However, the interior of the auricles with the purse-string sutures revealed only a tiny dimple at the site of ligature, in contrast to two shallow furrows at the ends of the suture lines with the clamp technique (Figs. 1c and 2c).

This study suggests that the simpler purse-string suture technique for closing the base of the left auricular appendage after mitral valvular commissurotomy provides a smoother endocardial surface than, and is probably preferable to, the clamp and suture method.

SUPERIOR MESENTERIC ARTERY EMBOLECTOMY

ROBERT B. ATWELL, M.D., Pittsburgh, Pennsylvania

OCCLUSION of the superior mesenteric artery by an embolus results in varying degrees of ischemia or gangrene of the bowel. This has long been considered to be one of the most lethal of all intra-abdominal catastrophes, and rightly so, as the mortality rate remains in excess of 80 per cent. Sporadic reports of survival after massive bowel resection have spurred surgeons to more vigorous treatment of this disease, but direct attack on the occlusion was not suggested until 1943 by Ryvlin. Successful embolectomy with recovery was first reported by Shaw and Rutledge in 1957. Stewart and associates and Miller and DiMare have subsequently reported cases, bringing to 4 the known survivors of superior mesenteric artery embolectomy.

In the period between 1955 and 1960, 14 autopsies were performed at the Presbyterian Hospital of Pittsburgh, Pennsylvania, in which mesenteric artery occlusion with gangrene of the bowel was found to be the major cause of death. This figure represents 1.0 per cent of the total autopsies performed during this period. Of these 14 occlusions, 5 were due to emboli. In only 1 patient was the mesenteric artery embolus the sole cause of death. It is immediately evident that the potential salvage from this disease is quite small. As demonstrated by Glotzer and Shaw the occlusion itself is usually surgically correctable, as the mesenteric artery approximates the femoral artery in size and lends itself easily to arteriotomy. Thrombosis of the artery distal to the embolus is unusual. The high mortality rate, therefore, is not due to the technical problems involved in embolectomy but to massive gangrene already present at the time of exploration and the almost invariable presence of severe heart disease.

Despite the apparent fact that early diagnosis and operation are essential for embolectomy to be successful, an example of an exception is presented in which 24 hours lapsed between embolization and successful removal of the embolus and which may stimulate more accurate and active surgical treatment of mesenteric artery occlusion.

From the Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh.

An 18 year old Negro male was admitted to the Presbyterian Hospital in August 1959 for evaluation of chronic rheumatic heart disease with atrial fibrillation. On 4 September 1959 percutaneous left atrial catheterization was performed. The data obtained revealed the presence of 4+ mitral insufficiency with 1+ mitral stenosis. He was not considered to be a candidate for operation on the mitral valve and was discharged on a low salt diet and digoxin.

On 8 September 1959, 1 day after discharge and 4 days after cardiac catheterization generalized weakness and mild abdominal pain suddenly developed. The pain became severe after the ingestion of several glasses of cold water and was accompanied by diaphoresis. He was taken to a local hospital where morphine and atropine was given prior to his transfer to the Presbyterian Hospital. When first seen he was in moderate abdominal distress with a blood pressure of 110/70 millimeters of mercury. The pulse was 120 and grossly irregular. Temperature and respirations were normal. Findings from examination of the head, neck, and lungs were normal. The heart was enlarged to the left anterior axillary line and to the right of the sternum. The pulmonic second sound was markedly accentuated and split. There was a systolic murmur and a middiastolic blowing murmur at the apex. There was mild to moderate diffuse abdominal tenderness with no localization or rebound tenderness. Bowel sounds were hypoactive. The liver was palpable 2 to 3 centimeters below the right costal margin but was nontender. No other abdominal masses were noted. The result of rectal examination was normal and the stool was guaiac negative. All peripheral pulses were present and equal.

The initial laboratory examinations revealed 400 milligrams per cent of urinary protein. The hematocrit was 42 per cent with a white cell count of 5,680. There were 68 per cent neutrophils, 19 per cent lymphocytes, and 13 per cent bands. Roentgenograms of the abdomen showed nothing remarkable. The electrocardiogram showed atrial fibrillation.

After admission there was an apparent improvement in the patient's condition and it was decided to treat him expectantly. The following day his white cell count had risen to 14,350. The abdomen was somewhat more tender and the peristalsis was obstructive in nature. Roentgenography of the abdomen was repeated and findings were interpreted as being "compatible with, but not diagnostic of, superior mesenteric artery occlusion." At 2 p.m. on 9 September 1959—almost 24 hours after the onset of symptoms—the patient passed two large bloody stools. He was immediately taken to the operating room.

At laparotomy the distal one-half of the jejunum and the entire ileum were found to be irregularly contracted, spastic, and edematous. The serosa was diffusely reddened and thickened but no areas of gangrene or perforation were present. The colon was not involved.

The colon was elevated and a good pulse was felt in the middle colic artery. The posterior parietal peritoneum was opened, exposing the retroperitoneal duodenum and the superior mesenteric vessels. The superior mesenteric artery was dissected free and encircled with heavy silk sutures. A longitudinal arteriotomy was made through which a catheter was easily slipped proximally into the aorta. However, the catheter could not be passed distally, and suction failed to evacuate the clot. This arteriotomy was closed and the jejunum was re-examined. Upon closer inspection of the marginal arteries it was possible to delineate the exact level at which visible pulsations ceased. The mesentery of the jejunum was opened and a pulseless jejunal branch was followed down to the superior mesenteric artery. At this point, approximately 6 centimeters from its emergence from under the pancreas and 4 centimeters distal to the first arteriotomy, an embolus could be seen and palpated. A second arteriotomy was made and the embolus was removed.

No appreciable change was noted in the bowel after embolectomy. Good pulsations were not restored but, since obvious gangrene was not present, it seemed reasonable to close the abdomen and to re-explore the following morning.

The abdomen was opened under local anesthesia 12 hours later and at this time it was apparent that all of the small intestine was viable. Pulses were present in the marginal arteries and the edema and spasticity were somewhat less.

Administration of broad spectrum antibiotics was started after the first operation, and 12 hours after the second operation the patient was heparinized. He tolerated these operations quite well and was taking oral feedings and passing flatus freely by the fifth postoperative day at which time the use of antibiotics and heparin was stopped. He was discharged on the fifteenth postoperative day and has remained free of gastrointestinal symptoms.

SUMMARY

Superior mesenteric artery embolectomy is a feasible and relatively simple procedure. Its success depends upon operation before gangrene is established and a thorough knowledge of the anatomy involved. In the case presented here the true nature and position of the occlusion was established only after a diligent search. It should be emphasized that arterial insufficiency of the gut may present a variety of gross appearances, from cyanosis or inflammation to a completely normal hue. The surgeon must not be misled by pulsations in the proximal artery or its early branches. A sharp level at which pulsations cease in the marginal arteries of the jejunum is an excellent guide to the embolus.

Recent experiences with retroperitoneal hematomas and their resultant complications in patients who have been given anticoagulants immediately after placement of aortic and iliac artery grafts leads one to agree with Klass that the use of anticoagulants should be deferred until the small transected vessels in the mesentery are securely clotted. The success of the embolectomy, as in all arterial procedures, lies not in the use of anticoagulants but in the reestablishment of unobstructed flow. The prevention of further emboli by anticoagulants, in my opinion, is a controversial point.

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THE SURGEON'S LIBRARY

Reviews of New Books

IT IS EXTREMELY IMPORTANT to be able to know the depth of anesthesia when a general anesthetic is being administered. About 10 years ago, through the use of the electroencephalogram, it was demonstrated that depth of anesthesia could be recognized, and servo-anesthetizers were tried and could be made to work. The book *Electroencephalography in Anesthesiology*[1] becomes important, for it shows not only patterns of old agents but also some of the newer ones. This is worthwhile reading for anyone who is concerned with general anesthetics. The authors are to be commended for preparing this book so that this particular phase of anesthesiology might be firmly and permanently established. —*John S. Lundy.*

BACON WROTE, "Reading maketh a full man, conference a ready man and writing an exact man." Richard P. Spencer, a Helen Hay Whitney Research Fellow in the Department of Biological Chemistry at Harvard Medical School, has set a high goal for himself in attempting to correlate structure, function, and pathology in terms of the basic sciences in his book *The Intestinal Tract*.[2] The publishers term the volume "the first available integrated account of intestinal structure, function, and pathology—a reference for clinical studies; an introduction to pertinent literature for scientists; a text for students." This is a worthwhile book to the extent that the author has achieved the goals outlined above. It is approximately 400 pages in length and contains nearly 1,800 references, which represent a most valuable summary of the literature.

The first section deals with the development and genetics of the intestinal tract and the methods for its study. The second section deals with normal intestinal function and its modifiers. The third and last section concerns disorders of intestinal function in which the author experienced difficulty in classifying the material. Successive chapters deal with the following topics: some effects of diet and psyche; ulcerative colitis, regional enteritis, and pseudomembranous enterocolitis; isotonicity and the dumping syndrome; potassium metabolism and protein loss.

Physiologic approaches to the study of gastrointestinal function are discussed in an uncritical approach "catalogue" fashion. On the other hand, the sections on biochemistry are longer and of more help.

The references at the end of each chapter are, in general, well chosen. They would be of more value for reference purposes if they were given in a consistent order.

The frequent use of the editorial "we" was disconcerting. However, the major deficiency of the book relates to the somewhat uncritical nature of its approach. For a publication to be of value to the reader, it should make available new information or present available knowledge in a more clear and readable fashion and, most of all, approach the subject in a discerning, critical fashion. For example, in discussing pseudomembranous enterocolitis, on page 282, the following statement is made without further comment: "There is also a report of administering normal intestinal bacteria by enema to restore the flora to the gut."

When the critical approach of the expert is missing from a book of this sort, the book represents little more than a poorly arranged reference list, and the reader is forced to make his own judgments after reading the primary sources of publication. Admittedly, we are not far enough along for definitive judgments in many areas. However, much interesting but essentially useless information, such as the nature of digestive processes in other creatures, is included in this volume.

In spite of these criticisms, the book represents a useful synthesis of what is known about many functions of the digestive tract and its appendages. The fact that the synthesis is uneven in spots, points up the difficulty for one man or a "one man author" to be an expert in all of these fields simultaneously.

—*E. Clinton Texter, Jr.*

THE AUTHOR of *Fractures, Dislocations, and Sprains*[3] has again produced a significant contribution to the field of orthopedics. The essential format of the book may properly be called an explained atlas of fractures and sprains. After a very excellent presentation of the general subject of fractures and sprains, together with the physiology of repair properly diagrammed, there is a discussion of the various types of fractures commonly seen in the regions of the body.

[1] ELECTROENCEPHALOGRAPHY IN ANESTHESIOLOGY. By Albert Faulconer, Jr., M.D., M.S., and Reginald G. Bickford, M.B., Ch.B., M.R.C.P. 90 pages, 35 illustrations. $4.75. Springfield, Ill.: Charles C Thomas, 1960.

[2] THE INTESTINAL TRACT. By Richard Paul Spencer, A.B., M.A., M.D. 411 pages, illustrated. $12.75. Springfield, Ill.: Charles C Thomas, 1960

[3] FRACTURES, DISLOCATIONS, AND SPRAINS. By Philip Wiles, M.S.(Lond.), F.R.C.S.(Eng.), F.A.C.S. 67 pages, 519 illustrations. $7.50. Boston: Little, Brown & Co., 1960.

Roentgenograms and diagrams of the pathologic anatomy of the various types of fractures are included together with the treatment preferred by the author. Details of the various manipulative techniques are classically described. Surgical intervention is clearly defined in the proper fractures without describing the surgical technique employed. The distinguished author, "the master of the well chosen word," has given us an excellent book which is complete without being redundant, and students and surgeons alike will appreciate the style in which it has been written.

—Harley M. Sigmond.

THE TITLE, *Gynecological Urology*,[4] is an excellent choice, for the editor has been most successful in his task of compiling a modern, comprehensive textbook on this subject.

It is also a true display of international medical cooperation, for which the editor should be commended. Thirty-one men from 8 countries contributed to make it a worldwide compilation of opinions and techniques regarding gynecologic urology. The editor has done an excellent job of reducing repetition to a minimum. Personal opinions and techniques emphasized by the various contributors are not overpowering in that divergent views are given and a fine bibliography follows each chapter.

The book is divided into 7 sections: (1) history; (2) anatomy, physiology, pharmacology; (3) genitourinary fistulas; (4) sphincter incontinence of urine; (5) urologic diseases of gynecologic significance; (6) effect of gynecologic conditions on the urinary system; (7) the urinary system in gynecologic surgery. Within these divisions, congenital, gynecologic, obstetric, surgical, radiologic, and urologic problems and complications are all thoroughly discussed.

A heavy, glossy stock has been used in printing the easily read, large and sharp type. Unfortunately, the illustrations vary in degree of clarity with the different authors but, for the most part, are clear and meaningful.

—Albert B. Gerbie.

CONTRIBUTIONS by 24 recognized physicians, primarily from the surgical faculty at Cornell University Medical College, Comprise the book *Surgery in the Aged*.[5] Its aim is to bring together in one volume the experiences of the New York Hospital-Cornell Medical Center group on this subject which is becoming increasingly common and important since the average life-span in American society now approaches 70 years or more and continues to increase with each passing decade.

What constitutes surgery of the aged and how does surgery of the aged differ from surgery in general? The authors have attempted to answer these questions by presenting the fundamental concepts in the initial 5 chapters. The physiologic and metabolic response to surgery is reviewed. Surgical infections are discussed, antibiotic therapy is summarized, problems in preoperative evaluation and preparation of the patient follow, anesthesia is evaluated, and postoperative care and management conclude the section on fundamental concepts. The general surgical concepts in the aged are so similar to those of surgery in general that no significant new material or concepts emerged in this particular section. The material, however, is clearly presented and well written.

The specific subject material is divided into 7 sections: (1) surgery of the thorax and thoracic wall; (2) cardiovascular surgery; (3) gastrointestinal surgery; (4) surgery of the biliary tract and liver; (5) genitourinary surgery; (6) surgery of special systems; (7) trauma and reconstructive surgery. Obviously, one cannot do justice to such broad and diverse fields in approximately 400 pages. Therefore, selection of the most frequent disorders in each of these categories is made, and the specific results and experiences of the contributor emerges. The selection of the chapters is good, and the topics covered include carcinoma of the lung, breast, esophagus, stomach, colon and rectum, biliary tree, prostate, and brain. Cardiac surgery is limited to the simpler forms of acquired heart disease, and the surgery of peripheral arteriosclerosis with the exception of abdominal aneurysm is scarcely mentioned. Appendicitis, diverticulitis, hernias, and intestinal obstruction are adequately discussed.

The inclusion of such specialties as urology, ophthalmic surgery, otorhinolaryngology, neurosurgery, trauma, and plastic and reconstructive surgery poses a curious problem. A specialist in any of these disciplines would not find these chapters adequate; the general surgeon, having felt the inroads of specialization on the scope of his work, views this subject matter with mixed emotions. On the one hand, he is delighted to believe that in the aged he can again aspire to treating other than abdominal disease with the general surgeon's knife; but, on the other, he is concerned that this segregation of disease by age, with the implication that significant problems of age alone bridge established specialties, may lead to the formation of another specialty in surgery, much like pediatric surgery. It might have been better to eliminate these specialties from the book but, then, it would have been necessary to expand the remainder into a text on general surgery.

The authors are to be commended for gathering together their experiences and results on general surgical problems in patients more than 60 years of age. But, they have rightly emphasized that it is the advances in general surgery that are important, and that these principles can be applied with sound surgical results to the 24,000,000 people who are now 60 years of age or older. The book will be a good reference work on the specific topics reviewed. It will be valuable primarily in libraries and in hospitals containing libraries for staff education. But with the exception of specific results in given diseases, the material is that of general surgery, and the reader seeking a modern text on general surgery should secure a more diversified and comprehensive work.

—Victor Richards.

[4]GYNECOLOGICAL UROLOGY. Compiled and edited by Abdel Fattah Youssef, M.B., D.S., D.G.O., M.Ch., F.I.C.S., with a foreword by Naguib Mahfouz. 890 pages, illustrated. $22.50. Springfield, Ill.: Charles C Thomas, 1960.

[5]SURGERY IN THE AGED. Edited by Frank Glenn, M.D., S. W. Moore, M.D., and John M. Beal, M.D. 534 pages, illustrated. $17.50. New York: McGraw-Hill Book Co., Inc., 1960.

IT WAS MY PRIVILEGE to review the first printing of *Synopsis of Pathology*[6] as well as to do so for the several intervening editions. My original thoughts and comments were definitely favorable and remain so with this, the fifth edition. Actually, only one small questionably adverse complication arises; the student relies so much on this text that he rarely uses the larger book edited by Anderson or the fine but more extensive ones of other writers.

As stated in the preface, as many changes as possible were made. The thought is ever in mind to keep the book concise. Older, less commonly encountered entities are deleted or are summarized more compactly, while new material has been added. The bibliography also has been decreased.

Some of the newly added lesions are pulmonary alveolar proteinosis, cat-scratch disease, and aldosteronism. Emphasis is also laid on the mycoses, viral hepatitis, mucoviscidosis, and Sheehan's and the carcinoid syndrome. Many others are also discussed.

Photomicrographs and photographs of gross specimens are used, and the tables and charts prove helpful.

There is an elaboration of the material on cytology which I welcomed. Perhaps more could have been written about radiation effects in view of the present furor. This could have been done at the expense of the space devoted to syphilis and the rare infections. More might have been included regarding staphylococcus (micrococcus) since this organism has grown so much more virulent. Consideration could also be given to the addition of some aspects of trauma. This may or may not be adaptable to the format.

None of the comments which I have made should be looked upon as critical. They are suggestions based upon questions asked by various medical students for whom the text is written. This, the fifth edition, may be recommended without reservation, as suiting the purpose for which it was written.—*M. C. Wheelock.*

IN THE MONOGRAPH, *Biomechanics of the Central Nervous System*,[7] the author presents the results of an investigation which has led him to a new conception.

He has demonstrated convincingly that the spinal cord does not move up and down in the spinal canal during flexion and extension of the spine. It is, instead, compressed with a corresponding increase in the cross sectional area during extension, and in flexion it is elongated and thin. Similarly, the roots do not move to and fro in their sheaths but are, also, stretched and compressed with motion of the spine. This three-dimensional physiologic deformation of the tissue is shared by all components of the hind brain, cord, and roots. The dura mater, likewise, folds and unfolds.

The cord is under physiologic tension because of its cranial, caudal, and lateral attachments. This tension is normally increased during flexion and decreased during extension. Consequently, any increase in axial tension is least well tolerated during flexion of the spine.

The author concludes from the findings that two important sources of injury to the cord and its roots are: (1) the loss of plasticity and elasticity of the tissue which may result from inflammation or sclerosis and (2) abnormal lengthening of the spinal canal which may be produced by pathologic angulation of the spinal column or from protrusions into the spinal canal. Both of these mechanisms increase the axial tension of the cord and this is most pronounced during flexion. Because the spinal cord does not have an up-and-down motion in the canal and since the dura folds and unfolds with the cord, friction may be discounted as an etiologic agent.

The work has been carefully and thoroughly done and the illustrations are good.

This book deserves to be read with care by all who are concerned with the treatment of the diseases of the nervous system. Although not primarily a clinical study, the findings and their interpretation have important clinical applications. —*S. J. Larson.*

THE NEW VOLUME of *Current Surgical Management II*[8] defines the controversies—many of them perennial—surrounding 16 surgical problems: polyps of the colon, duodenal ulcer and its complications, hiatal hernia, choice of operation for carcinoma of the head of the pancreas, detection of common duct stones, management of common duct wound, common duct stricture, management of normal gallbladder at sphincterotomy, pilonidal sinus, carcinoma of the breast, small bowel obstruction, arterial insufficiency of the lower extremities, thromboembolism, acute renal failure, preoperative preparation of the colon, prolapse of the rectum. With two exceptions, duodenal ulcer and carcinoma of the breast, these topics are entirely different from the 29 surgical controversies presented in Volume I.

Although such a book cannot resolve these controversial topics, it provides alternative and provocative viewpoints in equally persuasive and logical manners. It, therefore, combats the enemy of postgraduate education, namely, surgical provincialism. Both volumes are recommended to implement an enlightened and broadened viewpoint to the candidate for the board examination in surgery.

In my opinion, a few of the presentations in Volume II do not warrant the prestige of appearing in a textbook of surgery, i.e., "Roentgen Irradiation of the Stomach as an Adjunct to Medical Treatment of Peptic Ulcer," particularly when it is advised as acceptable treatment for gastric ulcer!

It will be interesting to peruse both volumes 10 years from now. Continued appraisal of these controversial subjects will be necessary from time to time to determine how they will ultimately be resolved. In my opinion, the first volume will occupy a more important place in the surgeon's library than the second.

—*Jack Matthew Farris.*

[6] SYNOPSIS OF PATHOLOGY. By W. A. D. Anderson, M.A., M.D., F.A.C.P., F.C.A.P. 5th ed. 875 pages, 418 illustrations. $9.25. St. Louis: C. V. Mosby Co., 1960.

[7] BIOMECHANICS OF THE CENTRAL NERVOUS SYSTEM; SOME BASIC NORMAL AND PATHOLOGIC PHENOMENA. By Alf Breig. 183 pages, illustrated. $8.50. Chicago: The Year Book Publishers, Inc., 1960.

[8] CURRENT SURGICAL MANAGEMENT II. A Book of Alternative Viewpoints on Controversial Surgical Problems. Edited by John H. Mulholland, M.D., Edwin H. Ellison, M.D., and Stanley R. Friesen, M.D., with contributions by 50 authorities. 348 pages, illustrated. $8.00. Philadelphia and London: W. B. Saunders Co., 1960.

BOOKS RECEIVED

Books received are acknowledged in this department and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

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SURVEY OF RESEARCH IN GESTATION AND THE DEVELOPMENTAL SCIENCES. By Jack Davies, M.D. 203 pages. $6.00. Baltimore: The Williams & Wilkins Co., 1960.

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